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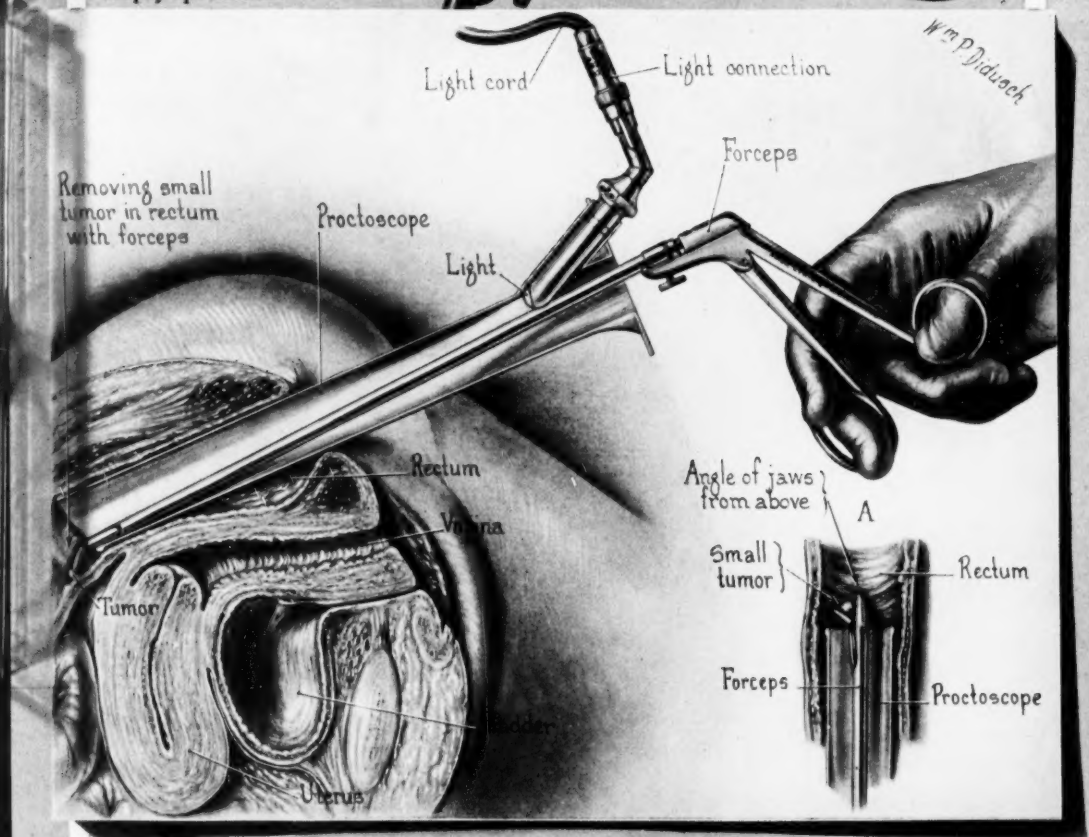

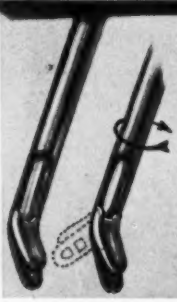

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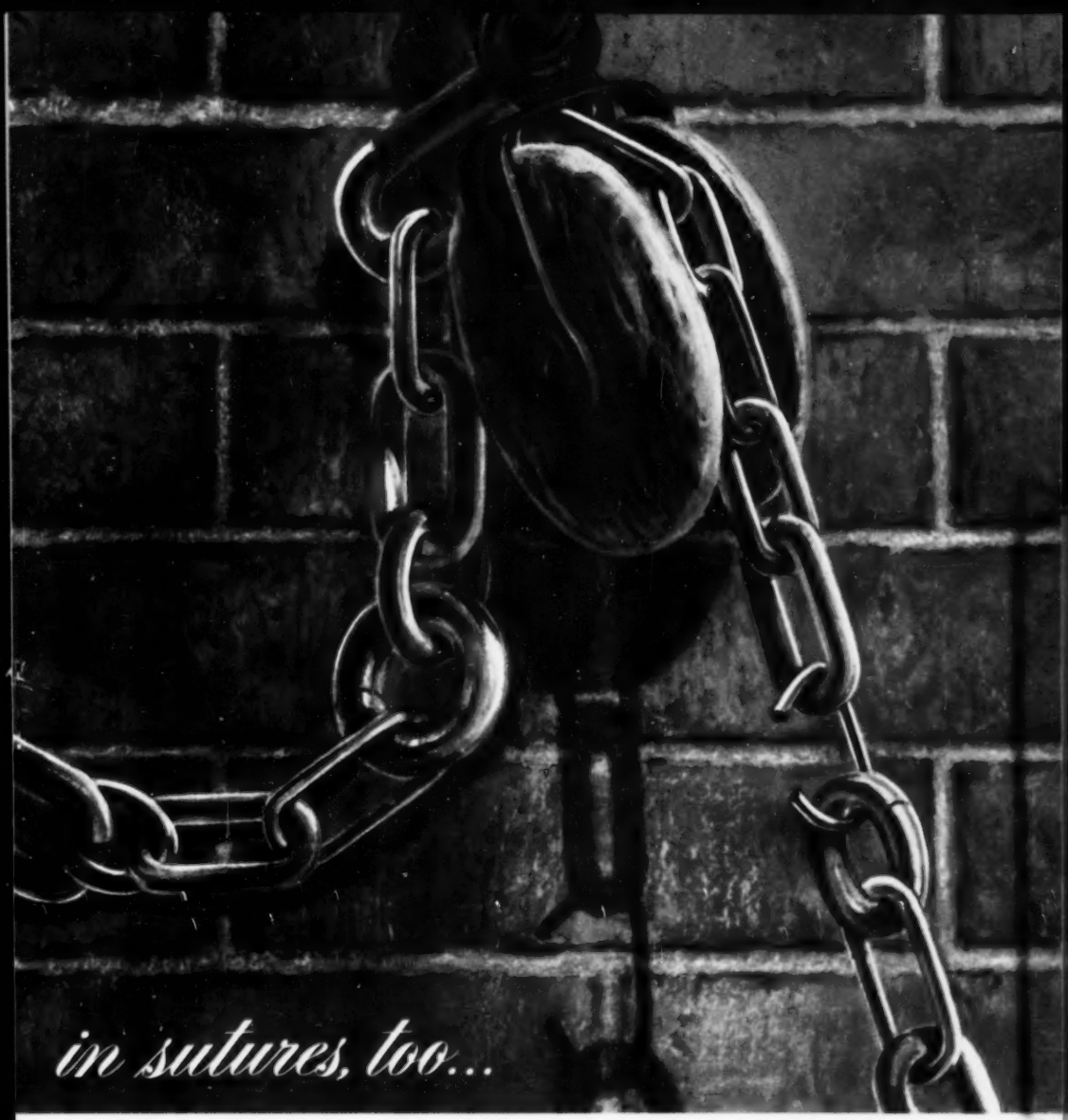

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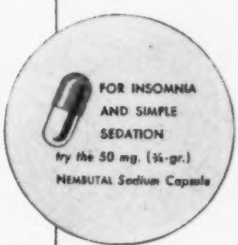


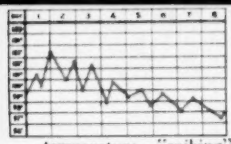
URINARY TRACT

Pyelonephritis

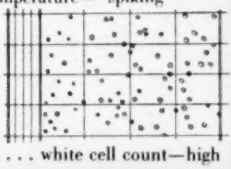
1 Pyelonephritis occurs most often in the young child . . .

commonest in the "diaper-age" female

2 The onset is sudden, usually with a chill . . .

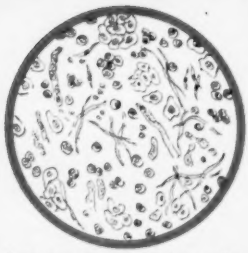


. . . temperature—"spiking"



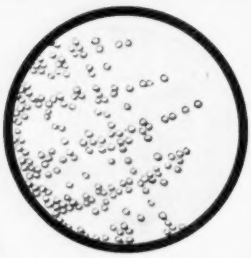
. . . white cell count—high

3 Always, pus cells and bacteria appear in the urine



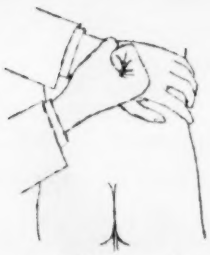
look for *clumps* of white cells in *catheterized* specimens

4 Culture determines pathogen. Mixed infection not uncommon.



in 8 out of 10 children, colon bacillus invades

5 Sometimes there is tenderness over the kidney region . . .



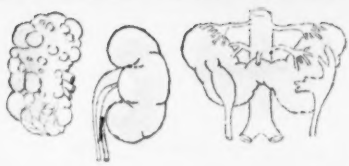
try the McKnight punch, or

palpation in C-V angle

6 . . . or abdominal pain and rigidity

suggestive of an acute abdomen

7 Look for a cause of urinary stasis.



in children, 75% have congenital malformation . . . others may have calculus, foreign body, neoplasm, ureteral spasm.

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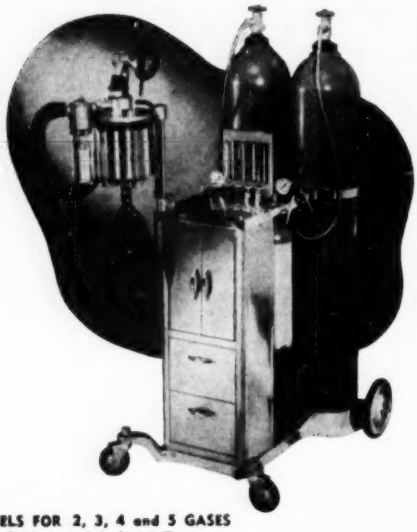

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VOLUME 65 AUGUST 1952 NUMBER 2

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Editorials

MEDICAL WRITING TO BE READ *

EDITORIAL

IN MEDICINE search should be followed by research. Mindful of this maxim the editors continue the search to make the A. M. A. ARCHIVES OF SURGERY more valuable to its readers and to lessen "the avoidable pain to authors, readers, and editors" sometimes caused, according to Howie, by the preparation of papers for publication in scientific journals. We are publishing in this issue excerpts from Dr. Howie's most interesting paper "On Writing to Be Read." One of his most pertinent comments is as follows: "A scientific paper should be as precise as a legal document, but it should also be as readable as a good short story." He discusses this from the authors' attitudes, the needs of readers, and the duty of editors. From a physician and head of the Pathology Division of the Rowett Research Institute, his comment that "scientific writers have much to learn from professional journalists about the needs of readers" seems particularly valuable, especially when he continues "writers who wish to have their work carefully read will do well to learn as much as they can both of the trade and the tricks of popular journalism." So we, besides reprinting excerpts from Howie's article, are publishing excerpts from a talk made by Mr. Harry Shaw, General Editor of Harper & Brothers, at a recent meeting of editors at the State Medical Journal Conference held under the auspices of the American Medical Association.

Mr. Shaw points out among other things that within our lifetime the automobile, motion pictures, radio, and television have had a terrific impact on our reading habits which "has made it inevitable that literature in general must have a far greater degree of sprightliness than it ever had." In his comments he cautions us to remember that "writing that does not communicate is not writing" and that writing should be kept simple. He quotes Sterne, "Writing when properly managed . . . is but another name for conversation," and Mumford, "A book has one leg on immortality's trophy when the words are for children and the meanings are for men."

You will find in Dr. Joseph Garland's editorial, a part of which we are also reprinting in this issue, this statement: "In its final state it [the medical paper] is crystal clear and informative and meets some need other than that of the author for publicity."

* Part of this title was borrowed from Dr. J. W. Howie. Excerpts from his manuscript are republished together with remarks of Mr. Harry Shaw, General Editor, Harper & Brothers, and excerpts from an editorial by Dr. Joseph Garland.

We think that as surgical readers and writers you will find much of interest and value in the thoughts and suggestions of these three men whose statements are published in part in this issue of the A. M. A. ARCHIVES OF SURGERY.

WALTMAN WALTERS, M.D.

ON WRITING TO BE READ *

J. W. HOWIE, M.D., ABERD.
GLASGOW, SCOTLAND

DOCTORS and scientists usually seem to dislike writing about their work: "I hate the writing-up," they often say. Perhaps it is the "up" that does the harm. If authors were content to write instead of writing-up, many mistakes might be avoided. Writing-up suggests that the author feels the need to do something beyond communicating his facts and thoughts.

Authors engaged in writing-up often seem to think that they must make a powerful impression. Some of this may arise from deliberate or unconscious imitation of works which are justly regarded as classics. Such works are classics because they contain valuable new facts and ideas, not because they may have been written in the grand manner, or perhaps directed with particular energy against someone whose views the author wished to contradict. Incidental attributes of this kind do not prevent papers with new and good information from becoming classics, but they are not the things that confer lasting value. The only incidental which has a truly classic quality is simplicity.

The author's job is to convey something from himself to his reader so well that the message conveyed will be gladly received and recognized for what it is. This is not a simple task; and it is not true that any set of words will do it, for there are no indifferent words. Every word of an article does good or ill: sections, paragraphs, sentences, phrases, words, or even parts of a word are evil if they can be done without. They make an article longer than it need be and the potential reader may decide that it is too long to attempt; they raise issues not connected with the main theme and so lessen the reader's enthusiasm and concentration; they irritate the fastidious and critical, the very people whose judgment and comments the author should particularly wish to enlist; and, worst of all, they may obscure the meaning. Editors who shorten articles often plead lack of space, but their real justification is the harm done by everything that can be done without.

For good reasons the presentation of a thesis is still highly regarded as useful training for a research-worker.

A thesis is seldom suitable for general reading, and editors who might gladly accept the essentials will reject the extras. . . . If a subject has been long neglected or greatly confused, a critical review of published work may be necessary to show the point of the author's own contribution. This is legitimate and acceptable; but wanton inflation of a reference list deceives nobody and irritates readers who recognize it for what it is.

"The essence of art is selection." This truth is sometimes regarded as inapplicable to the art of scientific communication. True, scientific articles must present

*The article from which these excerpts are taken was published in Lancet **1**:320-321 (Aug. 25) 1951.

the whole truth; to suppress inconvenient evidence is fraud. But if there is a great deal of inconvenient evidence, it is probably because the time has not yet come to present anything.

Every repetition, even of a successful experiment, need not be presented in detail. . . . A scientific paper should be as precise as a legal document, but it should also be as readable as a good short story.

Scientific writers have much to learn from professional journalists about the needs of readers. . . . Although readers of scientific periodicals are not surrounded by the same competing interests as readers of evening papers, their attention must be caught and their interest held. . . . The title of a scientific article deserves the author's careful thought; it should be freed of dull, inoperative words and should accurately indicate what interesting news the reader may expect. The first paragraph is equally important. My journalist friend assured me that having written an arresting title and a bright opening paragraph he felt sure of holding his reader. It is an excellent thing if the first paragraph of a scientific article tells what was done and why, and what the results were. This has long been recognized as essential in a summary, and it perhaps explains why some journals publish the summary at the head of the article. This may offend some as inelegant and too frankly utilitarian; but it is realistic.

Readers of scientific articles, however conscientious, have difficulty in reading all that they wish. However hard they try they will have to skim some articles very lightly, and this is one reason why the summary, tables, and illustrations must be clear and completely intelligible without the text. Writers who wish to have their work carefully read will do well to learn as much as they can both of the trade and the tricks of popular journalism.

Difficulty arises with articles containing good information badly presented. What can the editor do? His simplest and in some ways his least painful action is to reject such articles without explanation. Or he may send the article back to the author offering suggestions for amendment. . . . Editors of scientific journals, however, accept [this] as their duty

Being human, editors gladly publish articles written exactly in the style of their journal. These articles require no editing and they prove that the author has given care to their preparation.

LITERARY ASPECTS OF MEDICAL JOURNALISM *

HARRY L. SHAW
NEW YORK

AS I LOOKED over medical journals, I decided that they were just about half way between a trade journal and a general publication. A trade journal is obviously designed to make money for subscribers. I take it that medical journals have the ambition to help subscribers make money only incidentally.

More of you might conceivably spend more time with your medical journals if, possibly, they had a somewhat greater degree of literary quality and mechanical make-up.

*The excerpts from this article are taken from the Proceedings of the State Medical Journal Conference given under the auspices of the Board of Trustees and the Advisory Committee of the State Journal Advertising Bureau of the American Medical Association, Chicago, Nov. 12-13, 1951, pp. 19-27.

Persons who write, whether they write for medical journals, whether they read, or whether they edit medical journals, forget that writing that does not communicate is not writing . . . a book is not necessarily a book until it is read and that a medical journal is not a medical journal until it is in the hands of a reader.

First, I believe that we all should pay more than lip service to the problem of simplicity.

I know of no way of making it clearer that I think we sometimes use 10-dollar words when the brief, direct, simple method of expression would help . . . One of Chicago's most brilliant residents . . . when he writes for a popular audience, uses simple, direct words and he doesn't drum it down, either. He works over and over his writing to be certain that it is simple. . . .

Except for medical literature, all good writing has a conversational quality. . . . "Writing, when properly managed—," says Sterne and, being Sterne, he put in parenthesis "(As you can be sure I think mine is)— "is but another name for conversation."

Here is what Schopenhauer said: "A writer commits the error of subjectivity when he thinks it enough if he himself knows what he means and wants to say and takes no thought for the reader who is left to get at the bottom of it as best he may. The author must always be careful to remember that thought so far follows the law of gravity that it travels more readily from head to paper than from paper to head.

I think we ought to keep that in mind. Another literary aspect that is enormously important in this process of communication is that of being concrete. . . .

Another thing that I might suggest—and I grant you that this can't be done too frequently in medical journals; at least, I assume it can't—is to use the material tested qualities of narrative writing . . . I have done much reading in my time as an editor—I do a lot now—and from this I find that what sticks in my mind are the narrative incidents, the things that make a point, because they are applicable.

I think what I am trying to say is that communication can be helped greatly in terms of simplicity, in conversational quality, by writing with concreteness, by avoidance of subjectivity, and by the use of inference. . . .

All types of writing would be considerably improved if the authors were to incubate their material longer than they do. . . .

If, after they have finished the draft of an article, they would put it away on a desk or in the drawer and let it soak for as long as possible, they would be able to come back to it and polish it so it would be considerably more communicative.

There is a detachment that time gives in which you can see the faults, the glaring faults, stylistic and literary, in your own material after the passage of time that you can't see after you have just finished writing. . . .

The real art in the editing of medical journals or anything else consists of getting good material and the transmission of that information by all effort from the mind of the conceiver to the mind of the reader, and I think incubation will help greatly.

Third, I would like to say that there is no such thing as good writing—there is only good rewriting.

I once asked a well-known writer . . . how long it took him to write a profile for the *New Yorker*, four or five thousand words. He said, "Well, if I know my subject thoroughly, if I have talked to him or her and read everything he or she has ever written and talked to their friends and enemies and spent several weeks getting it all together and if I really know my subject . . ." and, as I would say,

thoroughly incubated, "then I can write six hundred words a day, but if I write that much, I will have to start over the next day," he says, "because, after twenty years of writing professionally for a living, I can write only five hundred words a day that will stand up."

Now suppose you say this to me. Suppose you say, "I am just getting across information. I don't have to have any literary quality." I say it does have to have this quality or it won't get across . . . the trouble with writing to please oneself is that oneself is frequently too easily pleased. You have no right to write only to please yourself, but you have to communicate with the reader, or so I think. . . .

I can't remember the titles that I read a few years ago, but I still believe that titles are more important to some persons than they are to the motion picture industry, and I wonder if, in terms of both typography and wordage, you could possibly improve the literary aspects of medical journalism by paying a little attention to merely the titles of the articles. . . .

According to most of the so-called experts, a title should be descriptive, and it should be arresting, attention-getting. . . .

I suggest occasionally doing a twenty or fifty-word summary of the essential part of the article which could appear preferably in the front of the article or, indeed, in the front of the advertising matter . . . we don't pay enough attention to getting started. We will do one of two things: we will start dully, "in medias res," as the Greeks would say, or we will wind up for a page or two before we really get to the heart of the thing. . . .

We will push into an article, and we will go as far as we can; stop, and start over on the next page. My own belief and my conclusion from what writing I have done is that you should go ahead and write, hell bent for leather, as fast as you can and pour out your ideas and information, let it soak and then come back and start the rewriting.

Thus, the article must evoke attention, interest, desire, and, finally, action, which might better be called reaction; that is, the intent of the reader to do something about it. . . .

If you look at the magazines today, you will find that the articles have grown increasingly shorter for the last twenty years.

I think that if, in medical journalism, the same thing is true that is true in general publishing, if they were cut a little more, they might be improved. . . .

I think that the literary aspects of medical journalism might be improved—and I say might be improved—if some of the articles were shortened, and perhaps more could be printed.

JINGLE BELLS *

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HERE IS what the editors would like for Christmas—and, indeed, for the whole new year.

They would like to receive a reasonable number of topflight new manuscripts—perhaps 250—from which they could make their choice, containing from 800 to

*The editorial from which these excerpts are taken was published in New England J. M. **245**:988 (Dec. 20) 1951.

4,000 words each, decently typed with double or triple spacing (including the case reports, footnotes and references) on a typewriter with a fresh ribbon. They would like to have the references limited to those of real significance, following accurately the style of the QUARTERLY CUMULATIVE INDEX MEDICUS. (The only impression that inflated "bibliographies" make is a bad one.)

Needless to say, perhaps, any paper that is fit to be published is written in as good English as the author can muster and is then rewritten at least twice, with a number of words discarded at each writing; for anything that is worth saying at all is usually said twice as well in half the number of words. Its tables and charts are few and simple and properly captioned. In its final state it is crystal clear and informative and meets some need other than that of the author for publicity.

After all, the only really valid reason for writing a scientific medical article is to present the results of useful investigation or seasoned experience, thus adding to the sum of medical knowledge, or to bring together and correlate existing knowledge in order to make it more easily available. Only occasionally is a single case worth reporting, to remind a journal's readers of the existence of some condition that may cause diagnostic confusion or to add to the knowledge of its treatment; it should be reported with the utmost brevity. A case report should always point a moral, whether or not it may adorn a tale.

OBSERVATIONS ON EFFECTS OF CORTICOTROPIN (ACTH) AND CORTISONE IN MANAGEMENT OF SOME POSTOPERATIVE SURGICAL PROBLEMS

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DETROIT

IN RECENT years, the pituitary-adrenocortical system has been shown experimentally and clinically to have an important and sometimes dominant role in the regulation of electrolyte,[1] carbohydrate,[2] protein,[3] and fat[4] metabolism, of hematopoiesis,[5] of tissue cellular reaction,[6] and of the enzymatic[7] and antigenic[8]

From the Division of General Surgery and Gynecology of the Henry Ford Hospital.

Read in part before the Section of Surgery, General and Abdominal, at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, June 13, 1951.

1. (*a*) Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15-66 (Jan.) 1948. (*b*) Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199-258 (Feb.) 1950. (*c*) Ingle, D. J.: The Biologic Properties of Cortisone: A Review, J. Clin. Endocrinol. **10**:1312-1354 (Oct.) 1950. (*d*) Mason, H. L.; Power, M. H.; Reynearson, E. H.; Ciaramelli, L. C.; Li, C. H., and Evans, H. M.: Results of Administration of Anterior Pituitary Adrenocorticotropic Hormone to a Normal Human Subject, ibid. **8**:1-14 (Jan.) 1948. (*e*) Fourman, P.; Bartter, F. C.; Albright, F.; Dempsey, E.; Carroll, E., and Alexander, J.: Effects of 17-Hydroxy-Corticosterone ("Compound F") in Man, J. Clin. Invest. **29**:1465-1473 (Nov.) 1950.

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3. Ingle.[1c] Mason.[1d]

4. Ingle.[1c] Mason.[1d] Fourman.[1e]

5. (*a*) Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adrenocorticotrophic Hormone (ACTH) in Man, Blood **3**:755-768 (July) 1948. (*b*) White, A., and Dougherty, T. F.: Effect of Prolonged Stimulation of the Adrenal Cortex and of Adrenalectomy on the Numbers of Circulating Erythrocytes and Lymphocytes, Endocrinology **36**:16-23 (Jan.) 1945.

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8. (*a*) Chase, J. H.; White, A., and Dougherty, T. F.: The Enhancement of Circulating Antibody Concentration by Adrenal Cortical Hormones, J. Immunol. **52**:101-112 (Feb.) 1946. (*b*) Fischel, E.: The Relationship of Adrenal Cortical Activity to Immune Responses, Bull. New York Acad. Med. **26**:255-260 (April) 1950.

systems of the body. Much evidence has also been produced that while the physiological integrity of the body is at all times dependent on the normal functioning of the pituitary-adrenocortical system, the adrenocorticotropic and adrenocortical hormones serve a purpose of particular importance in the defense of the body against noxious stimuli of all varieties.[9] The well-known hypothesis of the adaptation syndrome of Selye[10] endeavors to integrate this interplay of the manifold functions of the pituitary-adrenocortical system and the effects of nonspecific stimuli, or "stress," into a rational chain of physiological events.

On a priori grounds alone, one would assume that a surgical operation is equivalent to a physiological condition that acts upon the body as a stress stimulus calling into play the pituitary-adrenocortical system. Excellent, if not numerous, observations have been recorded to prove that the assumption is correct.[11] An inquiry into the possibilities of influencing the surgical stress reaction by administering one or another of the pituitary-adrenocortical hormones thus seems warranted. Unfortunately, however, the physiological variables of a surgical operation are so complex and the effects of the pituitary-adrenocortical hormones often so elusive as to make such an inquiry on the clinical level, in spite of the enormous volume of experimental data, a difficult one. Often, objective clinical methods of evaluation are inapplicable to the problems one faces and quantitative results impossible to obtain. At present, therefore, any such investigation must be merely exploratory and many of the conclusions reached, tentative. Nevertheless, a survey of clinical experiences in surgery with the pituitary and adrenocortical hormones is probably not untimely, since it may bring into focus those difficulties of the clinician that research in the fundamental sciences may attempt to solve, add to the store of information that is needed for the definition of the ultimate value of these agents, and perhaps set up signposts of danger in their use, which, because of their great promise and ready availability, seems to be growing more widespread.

CASE MATERIAL

Selection of Cases.—On grounds of their actions demonstrated in the laboratory and partly confirmed by clinical experience in other than surgical fields, the pituitary adrenocorticotropic hormone and cortisone may be used in the management of surgical problems for two purposes. First, one may aim by their administration at enhancing the effectiveness of the defense mechanism of the organism as a whole

9. Sayers, G.: The Adrenal Cortex and Homeostasis, Physiol. Rev. **30**:241-320 (July) 1950. Ingle.[1c]

10. Selye, H.: General Adaptation Syndrome and Diseases of Adaptation, J. Clin. Endocrinol. **6**:117-230 (Feb.) 1946.

11. (*a*) Roche, M.; Thorn, G. W., and Hills, A. G.: The Levels of Circulating Eosinophils and Their Response to ACTH in Surgery: Their Use as Index of Adrenocortical Function, New England J. Med. **242**:307-314 (March 2) 1950. (*b*) Dury, A.: Changes in Circulating Eosinophiles and Adrenal Ascorbic Acid Concentration After Agents Altering Blood Sugar Levels and After Surgical Conditions, Am. J. Physiol. **163**:96-103 (Oct.) 1950. (*c*) Eliel, L. P.; Pearson, O. H., and Rawson, R. W.: Postoperative Potassium Deficit and Metabolic Alkalosis, New England J. Med. **243**:471-478 (Sept. 28); 518-524 (Oct. 5) 1950. (*d*) Johnson, H. T.; Conn, J. W.; Iob, V., and Coller, F. A.: Postoperative Salt Retention and Its Relation to Increased Adrenal Cortical Function, Ann. Surg. **132**:374-385 (Sept.) 1950.

against nonspecific stress (such as the sum total of the trauma of a major operation). Secondly, one may attempt to influence favorably a specific pathologic process which is presumed to be susceptible to the action of these hormones.

It will be convenient to classify and discuss the cases of this study under headings corresponding to these two possible therapeutic aims, with the understanding that a truly rational therapeutic selection, for reasons to be shown, is not at present possible.

As regards the use of corticotropin (ACTH) and cortisone in nonspecific stress reaction (Groups 1A and 1B, Table 1), the first problem that arises is the establishment of criteria for the recognition of that type or degree of functional insufficiency of the pituitary-adrenocortical system which calls for hormone therapy.

The pituitary-adrenocortical insufficiency that may presumably concern the surgeon is practically always a relative one;[12] i. e., it represents an inadequacy of response in the pituitary-adrenocortical system to supernormal stimulation (such as surgical trauma may bring about). In contrast to absolute insufficiency, as seen in the addisonian syndrome, relative pituitary-adrenocortical insufficiency cannot be detected by clinical means. Concerning the laboratory methods devised for the estimation of the functional response of the pituitary-adrenocortical system, they are useful, but at present not wholly satisfactory as criteria on the basis of which cases suitable for hormone treatment can be selected. Among these one may cite the widely used four hour corticotropin [13] and epinephrine [14] tests devised by Thorn, which are excellent all-or-none indicators of the functional responsiveness of the pituitary system but which do not allow of quantitative interpretation.

Until further knowledge is gathered, one must adopt a rather empirical approach to the problem of selection in the first group of cases, i. e., in the group treated with corticotropin or cortisone for the nonspecific effects of these hormones against stress. In the cases assigned to this group, from clinical evidence, we assumed that a disproportion existed between the magnitude of the operative stress and the pituitary-adrenocortical reserve of the patient. According to the clinical evidence on which this assumption was based, these patients can be further divided into two subgroups. In one subgroup (Group 1A) belong the patients who in conventional terms [15] represented poor risks in relation to the proposed operative procedure but whose inferiority as risks was not due to a recognized organic disease, such as diabetes, arterial hypertension, or a nephropathy, but to some degree of debility, low-grade but long-standing malnutrition, advanced age, underweight, or obesity. In these cases corticotropin was administered throughout convalescence in an effort to determine whether stimulation of the adrenal cortex beyond that caused by the

12. Hume, D. M., and Moore, F. D.: The Use of ACTH, Cortisone, and Adrenal Cortical Extracts in Surgical Patients, in Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 2, pp. 289-309.

13. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005-1009 (July 17) 1948; correction, **137**:1544 (Aug. 21) 1948.

14. Recant, L.; Forsham, P. H., and Thorn, G. W.: Effect of Epinephrine on the Circulating Eosinophils, Federation Proc. **7**:99 (March) 1948.

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TABLE 1.—*Corticotropin and Cortisone in Surgical Complications*

1A.—Nonspecific Prophylactic Use

Case No.	Race	Sex	Age	Diagnosis	Associated Diagnoses	Operation	Indication for Hormone Therapy	Hormone Duration, Days	Therapy Dose of ACTH,* Mg.	Other Therapy	Course
1	W	M	63	Carcinoma of the stomach with long-standing pyloric obstruction	Malnutrition, dehydration; generalized arteriosclerosis	Subtotal gastrectomy (Hoffmeister-Finsterer)	Poor operative risk	8 7	335 480	Routine postoperative care; digitalis	Early congestive cardiac failure on 1st postoperative day; controlled by digitalization; otherwise smooth recovery
2	W	M	67	Chronic peptic ulcer of stomach	Obesity; generalized arteriosclerosis; secondary anemia	Subtotal gastrectomy (Billroth I)	Poor operative risk	4	210	Routine postoperative care; digitalis	Auricular fibrillation 1st postoperative day, stopped by digitalization; otherwise smooth course
3	N	M	56	Chronic peptic ulcer of stomach and duodenum	Malnutrition	Subtotal gastrectomy (Hoffmeister-Finsterer)	Poor operative risk	2 4	120 200	Routine postoperative care	Smooth recovery
4	N	M	51	Carcinoma of urinary bladder	Malnutrition, secondary anemia	Urinary cystectomy, prostatectomy, left inguinal colostomy; transplantation of ureters	Poor operative risk; extensive operation	4.5	275	Routine postoperative care	Smooth recovery for 16 days; intestinal obstruction on 16th postoperative day, relieved by surgery
5	N	F	30	Congenital polycystic kidneys	.....	Left nephrectomy; resection of left colon	Fair operative risk; extensive operation	1	50	Penicillin	Immediately after operation severe shock, then smooth recovery

1B.—Nonspecific Therapeutic Use

Case No.	Race	Sex	Age	Diagnosis	Associated Diagnoses	Operation	Indication for Hormone Therapy	Hormone Duration, Days	Therapy Dose of ACTH,* Mg.	Other Therapy	Course
6	W	F	51	Chronic sigmoid diverticulitis with perforations	Functioning transverse colostomy	Resection of sigmoid colon	Debility, fever, anorexia, extreme apathy	4.5	220	Chloromycetin, penicillin	Hormone therapy begun on 5th postoperative day; rapid improvement and smooth recovery; effect of ACTH on patient's appetite was noteworthy
7	W	M	63	Thrombosis of superior mesenteric artery	Generalized arteriosclerosis, arterial hypertension	Resection 26 ft. small bowel, jejuno-transverse colostomy	Profound shock, extremely poor general condition	1.5	600	Penicillin	Gradual downhill course; ACTH discontinued suddenly; disseminated arterial thrombi at autopsy on 6th postoperative day, 24 hr. after discontinuation of ACTH
8	W	F	..	Acute gangrenous appendicitis with perforation, generalized peritonitis	Recurrent acute small bowel obstruction due to adhesions	(1) Appendectomy, lysis of adhesions, resection segment of ileum; (2) lysis of adhesions, jejunostomy	Extreme debility (moribund)	1.5 3	60 Cortisone 360	Sulfadiazine, penicillin, streptomycin	Following administration of ACTH after 2d operation, the rapid worsening of patient's condition arrested; slow, complete recovery; effect of ACTH appeared dramatic
9	W	F	..	Strangulated left femoral hernia (of 7 days' duration)	Rt. pneumonitis, acute toxic nephritis, uremia	Exteriorization of gangrenous ileum	Extremely poor general condition	5	300	Penicillin, streptomycin, aureomycin	Slow but steady improvement to complete recovery; on 8th postoperative day, left popliteal phlebothrombosis, treated with heparin

* Corticotropin (ACTH) was given intramuscularly unless otherwise indicated.

operative stress was possible and whether, if present, the stimulation was a beneficial factor in the postoperative recovery. In the sense that the projected aim of the administration of the hormones was the prevention of postoperative complications and the promotion of a "smoother" postoperative course, the use of corticotropin in this class of patients may be termed "prophylactic." The second subdivision (Group 1B) of this group comprised cases in which a stormy convalescence ensued from multiple coincidental causes; the common denominator in these cases was the evident exhaustion of the patients' defensive reserve against the accumulated stress of the operation. The use of corticotropin and/or cortisone was, of course, entirely empirical and represented the application of a potent medicinal agent against apparently hopeless odds.

In the second main group of cases (Groups 2A to 2F, Table 2), on the whole the use of corticotropin and cortisone was based on more rational therapeutic grounds. In these cases the agents were used in the management of complications that, on the basis of reported clinical experience and the experimentally proved physiologic actions of the adrenocorticotropic and adrenocortical hormones, seemed susceptible to being favorably affected by exogenous stimulation of the adrenal cortex or by the injection of exogenous cortical hormone. These complications consisted of the following: postoperative sepsis, postoperative shock (hypotension), pulmonary edema, intravenous clotting, and hypersensitivity states of surgical importance. The application of the hormonal agents in Group 2 can be termed, in a very broad sense, specific.

The Choice of Hormonal Agents.—According to most available evidence, the administration of exogenous corticotropin reproduces the complete physiologic action of the endogenously secreted adrenocorticotropic hormone; i. e., it stimulates the entire spectrum of cortical steroids. Its action is in fact the controlled reproduction of the normal pituitary-adrenal cycle, provided only that a functionally responsive adrenal cortex is present. In this study, corticotropin was used in the great majority of cases, and resort was made to the administration of cortisone only if evidence was found (in poor eosinophile response and/or lack of the expected clinical changes) of absence of adrenocortical activation. A total stimulation of the adrenal cortex seemed particularly warranted in an investigation the aim of which often consisted of an inquiry into the protective functions of the adrenal cortex against nonspecific stress.

Methods of Study.—As the first step in the study of the nonspecific prophylactic action of the hormones (as defined in a foregoing paragraph) in a group of cases (Group 1A, Table 1), in addition to clinical observations, metabolic studies were carried out. The purpose of these studies was primarily protective, i. e., to detect early if the administration of the hormones causes harmful postoperative physiological alterations, and thus they were not of sufficient scientific rigor to be considered true electrolyte and fluid balance studies. Even so, however, they have furnished clinically useful data with respect to the postoperative metabolic behavior of the patients observed during corticotropin and cortisone medication. The studies in these cases were done in the following manner: Twenty-four hour urine collections were begun 24 to 72 hours before the date of the operation for the estimation

TABLE 2.—*Corticotropin and Cortisone in Surgical Complications*

Case No.	Race	Sex	Age	Diagnosis	Associated Diagnoses	Operation	Indication for Hormone Therapy	Hormone Duration, Days	Therapy Dose of ACTH,* Mg.	Other Therapy	Course
2A.—Hypotensive Oliguria											
10	W	M	62	Incarcerated left femoral hernia	Hypertension (250/140)	Hernia repair (spinal anesthesia)	Postoperative hypotension; persistent marked oliguria	4.5	425	Penicillin, streptomycin, blood plasma	Prompt diuresis after ACTH; B. P. returned to normal level; normal recovery; effect of ACTH is particularly remarkable in view of failure of other vigorous treatment
11	W	M	73	Urethral stricture; instrumental perforation of urethra	Generalized arteriosclerosis; hypertension (170/110)	Suprapubic cystostomy	Postoperative hypotension; marked oliguria	4	300	.....	Oliguria of 200 cc. in 24 hr.; B. P. 80/60 to 68/50; 2 hr. after ACTH B. P. 140/80; diuresis; normal recovery
12	W	F	59	Infaret rt. lower pulmonary lobe	Diabetic coma	.....	Hypotensive oliguria	1	75	.....	Admitted unconscious; persistent hypotension; B. P. 80/60; 15 cc. urine/24 hr.; after ACTH, B. P. 120/80, 500 cc. urine/24 hr.; recovery
2B.—Lower Nephron Nephrosis											
13	W	M	61	Multiple fractures and contusions	Traumatic shock, B. P. 80/54	Closed reduction and immobilization of fractures	30 cc. of urine daily for 3 days after admission	1.5 3	175 Cortisone 550	Parenteral fluids	No appreciable effect after ACTH for 2 days; then gradual improvement to recovery
14	W	M	66	Chronic duodenal ulcer	Duodenal fistula subhepatic abscess (postoperatively)	Subtotal gastrectomy (Hoffmeister-Finsterer)	After transfusion, 30 to 50 cc. urine daily	2	150	Parenteral fluids, antibiotics	Increase of urinary output to 600 cc. a day; patient died in 2 days
15	N	F	26	Incomplete abortion	Secondary anemia	.....	After transfusion, oliguria and hypotension	10	575	Parenteral fluids, antibiotics	Gradual return of renal function after 7 days
2C.—Thyrotoxic Crisis											
16	W	F	24	Diffuse thyroid hyperplasia with thyrotoxicosis (BMR + 63)	Acute follicular tonsillitis (streptococcus)	None	Patient in extremis, temp. 103.2 F., pulse 140, resp. 40.	3	260	Penicillin	Within 4 hr. of administration of ACTH, dramatic improvement; recovery
17	W	F	33	Diffuse thyroid hyperplasia with thyrotoxicosis (BMR + 56)	Acute follicular tonsillitis	None	Severe thyrotoxic crisis; temp. 104 F., pulse 140	8	330	Aureomycin, penicillin	Within 6 hr. of first dose of ACTH, marked improvement; recovery
18	N	F	15	Diffuse thyroid hyperplasia with thyrotoxicosis (BMR + 77)	.....	Subtotal thyroidectomy	Severe thyrotoxic crisis, temp. 104 F., pulse 154, resp. 40	2.5	225	I. V. glucose and strong iodine solution, U. S. P.	Within 2 hr. marked dramatic improvement; recovery
19	W	F	50	Diffuse thyroid hyperplasia with thyrotoxicosis	.....	Subtotal thyroidectomy	Prophylactic use; preoperative preparation inadequate; last preoperative BMR + 63	5.5	310	I. V. glucose and strong iodine solution, U. S. P.	Entirely smooth postoperative recovery

2D.—Sepsis

Case No.	Race	Sex	Age	Diagnosis	Associated Diagnoses	Operation	Indication for Hormone Therapy	Hormone Duration, Days	Therapy Dose of ACTH,* Mg.	Other Therapy	Course
20	W	M	38	Carcinoma of stomach	.....	Total gastrectomy with transposition of ileocolic segment	Generalized peritonitis (severe toxic symptoms)	...	...	Penicillin, streptomycin, aureomycin	Progressively downhill, death on 11th postoperative day; autopsy revealed presence of severe acute pancreatitis traumatic, probably site of origin of peritonitis
21	W	M	57	Acute sigmoid diverticulitis with perforation	.....	Drainage of paracolic abscess	Generalized peritonitis (severe toxic symptoms)	3	180	Penicillin, streptomycin	Drainage failed to improve general condition, temperature continued high; after ACTH, rapid recovery
22	W	F	42	Infected abortion, pelvic peritonitis, abscess	.....	None	Severe toxic symptoms	5	250	Penicillin, streptomycin, blood transfusion	After ACTH, restlessness and anorexia improved; gradual recovery; pelvic inflammatory process remained localized
23	...	..	..	Infected abortion, pelvic peritonitis	.....	None	Severe toxic symptoms	5	475	Penicillin, streptomycin, blood plasma	ACTH given in 3 courses; during administration improvement; afterwards relapse; on 16th hospital day, pelvic abscess drained
24	W	M	69	Carcinoma of urinary bladder	Generalized arteriosclerosis	Cystoscopy, accidental perforation of urinary bladder	Pelvic peritonitis with severe toxicity	3	225	Penicillin, streptomycin	Prompt improvement after ACTH; no evidence of spread of inflammatory process

2E.—Operative Shock

25	W	F	38	.....	.....	Vaginal hysterectomy (cyclopropane anesthesia)	Persistent hypotension (68/30)	16 hr. 2	100 125	1,000 cc. saline; 500 cc. whole blood	Clinical signs of shock much improved, B. P. rose to 100/60 after ACTH; (intravenous therapy ineffective prior to ACTH)
26	W	F	47	Carcinoma of uterine cervix	.....	Radical hysterectomy (ethylene ether anesthesia)	Persistent hypotension (76/48)	1 ...	10 I. V. 60	10 mg. drinalfa,® ♦ 500 cc. blood	Definite improvement after ACTH was given; B. P. 100/80; (pressor substance and blood transfusion ineffective prior to ACTH)
27	W	M	44	Carcinoma of stomach	.....	Subtotal gastrectomy (fractional spinal anesthesia)	Persitent hypotension (60/30)	1 hr.	10 I. V.	10 mg. drinalfa,® 0.25 mg. phenylephrine hydrochloride	I. V. administration of ACTH in 500 cc. saline was followed by rise of blood pressure to 100/60; (therapy prior to ACTH administration apparently ineffective)
28	W	F	63	Chronic duodenal ulcer	.....	Subtotal gastrectomy (fractional spinal anesthesia)	Hypotension (80/65)	...	10 I. V.	Blood transfusion; 10 mg. drinalfa,® 1.0 cc. methoxamine hydrochloride	I. V. administration of ACTH without effect for 1 hr.
29	...	..	..	Chronic duodenal ulcer	.....	Subtotal gastrectomy (fractional spinal anesthesia)	Hypotension (95/70)	...	10 I. V.	Blood transfusion	I. V. administration of ACTH ineffective for 1 hr.

TABLE 2.—*Corticotropin and Cortisone in Surgical Complications—Cont'd.*

2F.—Acute Pulmonary Edema

Case No.	Race	Sex	Age	Diagnosis	Associated Diagnoses	Operation	Indication for Hormone Therapy	Hormone Duration, Days	Therapy Dose of ACTH,* Mg.	Other Therapy	Course
30	W	F	30	Rheumatic heart disease with mitral stenosis, mitral insufficiency; aortic stenosis, and aortic insufficiency; pregnancy 1½ mo.	.....	Hysterectomy (ether anesthesia; Trendelburg position of 15° for 40 min.)	During last 5 min. of operation slight lung edema growing severe with rhonchi and inspirational and expirational rales; B. P. 80/50	...	25	None	20 min. later respiration better; in 40 min. no rhonchi, few expirational rales; patient made uneventful recovery
31	W	F	49	Portal cirrhosis with esophageal varices; hematemesis	.....	Portacaval shunt	Postoperative bleeding; received 14 pt. of blood with development of lung edema; inspirational and expirational rales, foaming	...	50 × 2	(1) Oxygen tent; (2) 0.8 mg. lanatoside C; (3) tourniquets	No effect in 45 min. from lanatoside C; complete relief in 2 hr. after ACTH; patient died in 6 hr. of liver failure
32	W	F	49	Rheumatic heart disease with mitral stenosis and mitral insufficiency; auricular fibrillation; hypertension	.....	Commissurotomy	In operation ventricular fibrillation for 20 min.; remained unconscious; lung edema with inspirational and expirational rales, rhonchi; cyanosis	..	25 × 2	(1) Aminophylline 3¾ gr., I. V.; (2) oxygen under pressure; (3) stellate ganglion block	No effect from measures (1), (2), and (3); complete relief in 40 min., patient died with ventricular fibrillation
33	N	M	53	Flash burn, second and third degree, 65% upper body, arms, head and neck	.....	Sterile dressing in emergency room	On admission, cyanosis, dyspnea, inspirational and expirational rales; foaming	...	50	None	Complete relief in 80 min.; patient died in 5 days of effect of burns
34	W	F	59	Uremia, chronic nephritis	.....	.....	Cyanosis, dyspnea, inspirational and expirational rales, rhonchi; foaming	...	25 × 2	None	Improved in 90 min.; patient died in 3 days of uremia

* Corticotropin (ACTH) was given intramuscularly unless otherwise indicated.
† Drinalfa® is *d*-desoxyephedrine hydrochloride.

of total urinary output, total urinary nitrogen, creatinine, sodium, potassium, chloride, and 17-ketosteroids. On the day preceding the operation, a 4-hour Thorn test [13] was performed, and eosinohpile counts were done frequently thereafter. The levels of the same electrolytes as listed for the urine were determined daily or at frequent intervals on fasting blood samples; in addition blood carbon-dioxide-combining power, albumin-globulin ratio, fasting blood sugar, liver function, and nonprotein nitrogen were estimated at intervals. Drainage fluids were collected, measured, and occasionally analyzed for the same electrolytes as the urine. These studies were continued for five to seven days postoperatively or longer if the patient's recovery was not considered progressing well by that time. Clinical observations were recorded regarding the patient's progress, with special attention to the possible effects of corticotropin or cortisone on the patient's appetite, feeling of well-being, or psychic changes. Corticotropin [16] was administered in daily doses of 60 to 120 mg. divided into six hourly intramuscular injections of from 15 to 30 mg.; occasionally single doses of from 10 to 15 mg. of corticotropin in 500 cc. of 5% dextrose or isotonic sodium chloride solution were injected intravenously. The dose of cortisone was from 100 to 300 mg. daily, given intramuscularly in doses of from 50 to 100 mg. three times daily.[17] Rarely, larger doses were given. Intravenous fluids, antibiotics, and other medicines, as well as diet, were administered in the routine manner established for cases of the given type. In a small number of cases, the same plan of studies was carried out, as described above, with the purpose of giving corticotropin or cortisone only if an adverse turn in the patient's postoperative course should call for their use. It was thought that, if studied in large enough numbers, these cases could serve as controls.

Similar studies were carried out in cases of postoperative anuria and oliguria (Groups 2A and 2B).

In cases of intravenous clotting (Group 2F) the following special laboratory investigations were made: prothrombin time (Quick [18]), diluted prothrombin time (Shapiro [19]), and protamine titration.[20]

In the remaining cases, metabolic or other special studies were only occasionally applied, and the observations were mainly clinical. The dosage of corticotropin and cortisone, which varied within the range mentioned above, was controlled on the basis of clinical progress, eosinophile counts, and urinary ketosteroids. In instances of urgent complication, when the hormones had to be applied without forewarning (thyroid storm, hypersensitivity states, acute pulmonary edema), often all studies had to be dispensed with.

16. The corticotropin used in this study was, in most cases, the product of Armour (Standard LA-1-A); for part of the study the hormone was obtained through the courtesy of Parke, Davis & Company.

17. Cortisone was administered as cortone® acetate (Merck).

18. Quick, A. J.: A Quantitative Estimation of Prothrombin, Am. J. Clin. Path. **15**:560-566 (Dec.) 1945.

19. Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: A Procedure and Clinical Interpretations, Proc. Soc. Exper. Biol. & Med. **50**:85-90 (May) 1942.

20. Allan, J. G.; Moulder, P. V.; Elghammer, R. M.; Grossman, B. J.; McKeen, C. L.; Sanderson, M.; Egner, W., and Crosbie, J. M.: A Protamine Titration as an Indication of a Clotting Defect in Certain Hemorrhagic States, J. Lab. & Clin. Med. **34**:473-476 (April) 1949.

GROUP 1A: NONSPECIFIC PROPHYLACTIC USE OF ACTH AND CORTISONE (TABLE 1)

Three of the cases (Cases 1, 2, and 3) making up this group were somewhat alike: All three patients had subtotal gastric resection and represented about the same poor, or at best fair, degree of operative risk. The patients in Cases 4 and 5 were even more inferior risks and were subjected to operations of greater magnitude (total urinary cystectomy, left nephrectomy, and resection of left colon). Case 5 is unlike the other cases of the group with regard to the dosage of corticotropin. While in Cases 1 to 4 the doses of this hormone (and in Case 3, of cortisone) were of definite therapeutic size (although in Case 2 barely so), the patient in Case 5 received only 50 mg. of corticotropin divided in two doses. The long-term effects of such small amounts of the hormone are highly questionable.

In evaluating the effects of the adrenocorticotropic and adrenocortical hormones in these cases, one would wish to find answers to the following questions: (1) whether the hormonal agents improved the postoperative recovery by preventing expected complications and by shortening the period of convalescence, and (2) whether the patients under such treatment manifested physiological changes (within the range of detection of the methods of study used) that can have been caused by the action of the administered hormones.

As regards the first question, owing to the small number of cases observed, an answer obviously cannot be given. The assessment of the value of these agents in postoperative recovery, i. e., of their protective action against the stress of operative trauma, calls for a large-scale statistical investigation.

With respect to the second question, divers observations were made that are of some interest.

The antipyretic action of corticotropin (well known from experience with its use in febrile diseases, such as lobar pneumonia) was noted with a fair degree of consistency. It was the impression of those in charge of these cases that the patients manifested a degree of cooperation and a mental serenity in face of the usual trials of postoperative convalescence that were greater than usually seen. Euphoria was not observed. Since all patients had surgical procedures involving the gastrointestinal tract, the effect of the hormonal medication on their appetite is impossible to judge. (The significance of the foregoing scattered observations is strengthened by the fact that they were recorded also in a number of other cases to be described in subsequent paragraphs.)

Since corticotropin and cortisone have been shown in the laboratory to inhibit many cellular reactions essential in tissue repair,[21] e. g., fibroblastic growth, fibrin exudation, and the formation of histiocytes, it is perhaps significant that wounds of the abdominal walls healed without any evidence of impairment.[22] Since no sign

21. Baker, B. L., and Whitaker, W. L.: Interference with Wound Healing by the Local Action of Adrenocortical Steroids, Endocrinology **46**:544-551 (June) 1950. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, K.; Blunt, J. W., and Lattes, R.: The Effect of ACTH and Cortisone on Connective Tissue, Bull. New York Acad. Med. **26**:251-254 (April) 1950. Taubenhaus.[9]

22. Baxter, H.; Schiller, G., and Whiteside, J. H.: The Influence of ACTH on Wound Healing in Man, Plast. & Reconstruct. Surg. **7**:85-99 (Feb.) 1951. Scheinberg, S. R., and Saltzstein, H. C.: Prevention of Intra-Abdominal Adhesions by Cortisone and ACTH, Harper Hosp. Bull. **9**:6 (Jan.-Feb.) 1951.

of intraperitoneal escape of intestinal contents appeared in any of the cases, this must be likewise true of the anastomotic suture line.

The alterations in electrolyte metabolism (Chart 1) were similar to those seen in patients after major surgical procedures without hormonal treatment.[23] This was a finding somewhat contrary to expectations. It had been presumed that the sodium and chloride retention and potassium diuresis in the immediate postoperative period would be accentuated. On this assumption, potassium was administered in larger than customary doses, unnecessarily, as it later became apparent.

No definite evidence was discovered in these cases that the administration of corticotropin or cortisone had any detrimental effects. In Case 2, very questionable signs of phlebothrombosis of the extremity were noted on the 13th post-

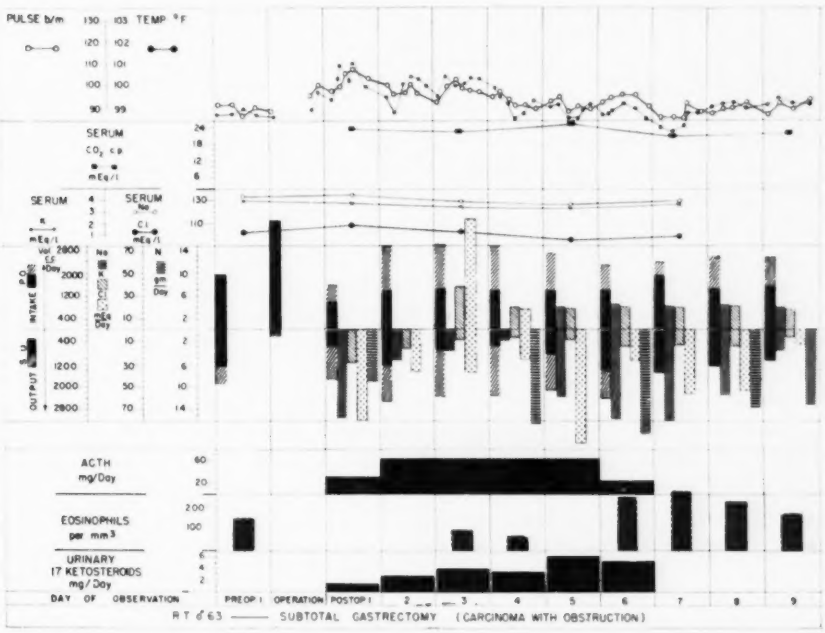

Chart 1 (Case 1, Table 1).—Postoperative use of corticotropin (ACTH). *p*, parenteral intake; *o*, oral intake; *s*, suction output; *u*, urine output.

operative day, or 8 days after the discontinuation of the use of corticotropin. In Case 5, more conclusive evidences of phlebothrombosis appeared 20 days after the last dose of hormone was administered. It is most unlikely that the hormonal medication had any causal relation to these complications.

GROUP 1B: NONSPECIFIC THERAPEUTIC USE OF CORTICOTROPIN AND CORTISONE (TABLE 1)

The patients in this group were not expected to recover when the decision was made to treat them with corticotropin. At that time, they all presented, with

23. Meyer, C. A.: Acute Temporary Changes in Renal Function Associated with Major Surgical Procedures, Surgery **27**:198-207 (Feb.) 1950. Johnson.[11d]

minor variations, the picture of the patient dying of the "physiologic exhaustion" of accumulated nonspecific insults.

In Case 6, one dealt with a grave postoperative exhaustion that is difficult to define. In Cases 8 and 9, the main physiologic disturbance was a severe grade of mineral and organic metabolic disturbance from long-continued intestinal obstruction, made worse, particularly in Case 9, by the presence of infection. None of these damages were irreparable and their correction was undoubtedly mainly the result of the supportive and corrective measures (intravenous fluids, blood transfusion, and antibiotic drugs) that were applied. What role corticotropin played in the ultimate favorable outcome cannot be said with assurance. It was the impression of those who observed the cases that the hormone was helpful in "turning the tide." There is some objective evidence supporting this opinion in the improvement of the vital signs in close time sequence to the administration of the hormonal agent.

The circumstances in Case 7, in contrast to the ones just discussed, were somewhat different. The extensive multiple arterial thrombotic episodes were unalterably fatal. Two facts in this case, however, require further comment. First, mainly because of ill-applied enthusiasm, very large doses of corticotropin were used (up to 600 mg. in one 24-hour period) which seemed, however, to bring about a rather dramatic temporary improvement in the patient's general condition. The large doses of hormone, however, in the last two or three antemortem days somewhat beclouded the gravity of the progression of the intra-abdominal disease. Secondly, the exact etiology of the multiple arterial thromboses remained somewhat obscure even after a postmortem examination. It was not definitely decided whether the cause of the formation of thrombi was an unrecognized disturbance in the clotting mechanism of the patient that had been present preoperatively and had initiated the thrombosis of the mesenteric artery or whether the excessive doses of corticotropin may have sufficiently altered the clotting factors to bring about spontaneous thrombosis. As will be seen below, an excessive dosage of corticortopin may enhance an intravascular clotting, and, thus, on consideration of the whole evidence, the harmful role of corticotropin in this case cannot be excluded.

GROUP 2: SPECIFIC THERAPEUTIC USE OF CORTICOTROPIN AND CORTISONE (TABLE 2)

A. Postoperative Hypotensive Oliguria.—In discussing postoperative renal failure, we make a distinction between oliguria (or anuria) occurring in refractory shock in the absence of recognizable renal tubular damage and lower nephron syndrome in which the renal tubules are injured. Undoubtedly, this differentiation cannot always be made accurately. In hypotensive oliguria, the cardinal physiological aberration is presumably decreased glomerular plasma flow and lowered filtration pressure.

In Cases 10 (Chart 2) and 11, an impairment of the urinary output appeared after surgical procedures that caused a persistent fall in blood pressure. In Case 12, oliguria developed during shock that apparently had been associated with a large pulmonary infarct, a rare cause for such an episode. This case, though not surgical in its etiology, is included in this series owing to its implications of interest to the surgeon.

Clinically, all three patients had prompt improvement of urinary flow within a few hours after the commencement of corticotropin administration. The changes were particularly prompt and marked in Case 10 (Chart 2) in which the urinary excretion of nitrogen and electrolytes was followed quantitatively during hormone therapy. In assigning credit for the improvement to the action of corticotropin, one must bear in mind that the large majority of patients with hypotensive oliguria recover with no treatment other than careful avoidance of overhydration and maintenance of a fairly normal blood electrolyte pattern. It is probably correct to say, however, that the recovery in such circumstances would not be as dramatic as

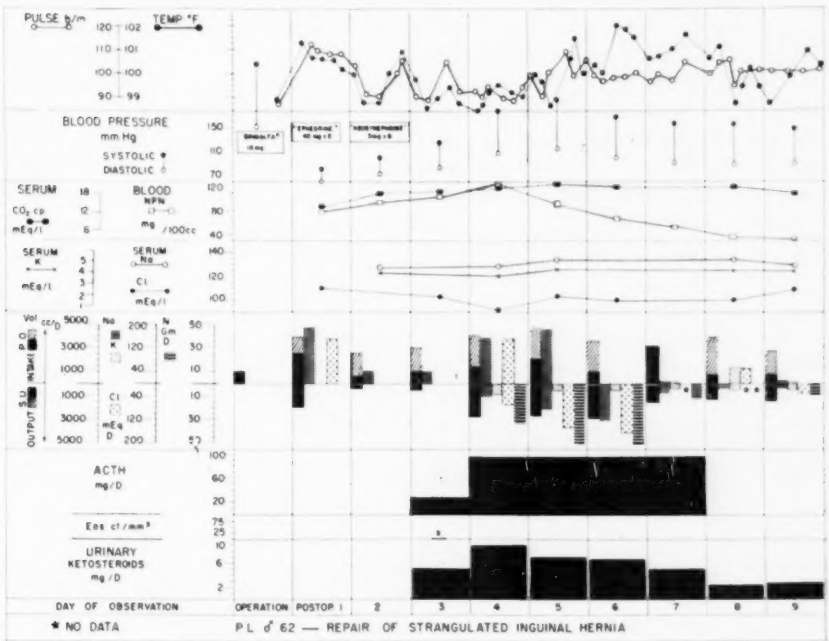

Chart 2 (Case 7, Table 2).—Clinical course and results of corticotropin in postoperative oliguria.

observed in these cases, nor would one expect such a rapid clearance of nitrogenous wastes and retained electrolytes as seen in Case 10. Moreover, in Case 10, a deliberate delay of 48 hours was allowed before administering corticotropin, during which usually potent vasopressor substances were administered and a transfusion of 500 cc. of blood was given without effect on the blood pressure or urine output. At least in this one case, the evidence seems quite convincing that the hormone had a corrective effect on the impairment of renal function.

The precise manner in which this action exerted its influence is difficult to define. From previous work on the effect of corticotropin on renal function, one may speculate that it was the resultant of several changes. The elevation of blood

pressure [24] with an increase in glomerular filtration pressure,[25] decreased tubular excretion,[25a] and perhaps changes in the permeability of the glomerular capsule all may have played a part in bringing about diuresis.

B. Lower Nehron Nephrosis.—While Case 15 is a clear-cut instance of lower nephron injury following a severe blood transfusion reaction, the nature of renal damage in the other two cases is less well defined. It is possible that the patient in Case 13 had some trauma directly affecting his kidneys. In Case 14, in addition to the transfusion reaction, there were other nephrotoxic factors (severe intra-abdominal infection).

The effects of corticotropin (and cortisone in Case 13) were inconsistent. In Case 13, after a lapse of time considerably longer than observed in the hypotensive oliguria cases following the commencement of hormonal therapy, slow diuresis appeared with concomitant outpouring of nitrogenous wastes and electrolytes. After the appearance of urinary flow, the behavior of the patient was rather like that in Case 10. In Case 14, the volume of urine increased promptly, but the blood non-protein nitrogen continued to rise. The patient died of multiple causes of which uremia was only one, although perhaps the main one. The recovery in Case 15 was characterized by the slow return of renal function seen in cases of lower nephron syndrome with adequate powers of tubular regeneration. It was not influenced by corticotropin therapy.

Claims have been made, largely of theoretical nature, that corticortopin and cortisone enhance tubular healing in lower nephron nephrosis by reducing the edema of the tubular epithelium and by protecting the latter against toxic insults. The evidence of the observations in this small series does not support this view. In only one case (Case 13) was there proof that corticotropin and cortisone may have influenced favorably the course of the disease, and in this instance the exact type of renal damage was not clear.

C. Thyrotoxic Crisis.—Case 16 represents an instance of the use of corticotropin both in the treatment of nonsurgical thyroid storm and in the pre- and post-operative management of severe thyrotoxicosis in which crisis is feared. Case 17 is an example of the application of corticotropin in the treatment of nonsurgical thyroid storm. In Case 18, the hormone was employed with the aim of controlling an established thyroid crisis, while in Case 19, it was used prophylactically before and after thyroidectomy on a patient who could not be satisfactorily prepared for the surgical procedure.

In the opinion of the attending staff, in each instance of application the hormone seemed to be beneficial. In Case 16 during the second thyroid storm brought on

24. Brust, A. A.; Ransohoff, W., and Reiser, N. F.: Blood Pressure Responses to ACTH and Cortisone in Normotensive and Hypertensive Subjects in the Resting State and During Autonomic Blockade with Tetra-Ethylammonium Chloride, J. Clin. Invest. **30**:630 (June) 1951.

25. (*a*) Green, D. M.; Farah, A., and Klemperer, W. W.: Mechanisms of Desoxycorticosterone Action: Renal Effects of the Water-Soluble Glycoside, Endocrinology **47**:281-288 (Oct.) 1950. (*b*) Ingbar, S. H.; Relman, A. S.; Burrows, B. A.; Kass, E. H.; Sisson, J. H., and Burnett, C. H.: Changes in Normal Renal Function Resulting from ACTH and Cortisone, J. Clin. Invest. **29**:825 (June) 1950. (*c*) Earle, D. P.; Alexander, J. D.; Farber, S. J., and Pelligrino, E. D.: Observations on the Relation of Renal Function Changes to the Electrolyte and Glycosuric Effects of ACTH, in Proceedings of the Second Clinical ACTH Conference. Philadelphia, The Blakiston Company, 1951, Vol. 1, pp. 139-147.

by a severe infection, it was generally believed that the patient's life was saved by the administration of corticotropin. While the very similar critical episodes in Cases 17 and 18 were not so devastating, the condition of these patients was also precarious. The postoperative course of the patient in Case 16, who had gone through two thyroid crises of the utmost severity and whose thyrotoxicosis just before operation was still very marked, and that of the patient in Case 19 who had shown no response to the measures of prepostoperative preparation, surprised everyone by its benignity.

Yet, there are circumstances in all cases that weaken the evidence that corticotropin was the decisive factor in the ultimate recovery. All patients, in addition to corticotropin received other medicines, the effects of which cannot be separated from the alleged action of the hormone. This is particularly true of the incidents of thyroid storm brought on by severe acute infection (Cases 16 and 17) in which rather heroic doses of antibiotics were used. We have not had occasion to resort to the use of corticotropin as the sole medicinal agent in treating thyroid storm. As in many other examples of its use, in judging the effectiveness of corticortopin in thyroid crisis the operation of chance also must be taken into consideration. Since in even hopelessly desperate cases patients do at times recover under conventional management, the element of chance will not be ruled out until larger statistical material is available for analysis.

The theoretical considerations by which the use of corticotropin in thyroid crisis may be rationalized are not entirely convincing. Although evidence has been presented that the administration of corticotropin inhibits the uptake of iodine by the thyroid gland [26] and lowers the basal metabolic rate in some thyrotoxic patients, this appears to be a variable effect.[26c] It has been suggested that when depression of thyroid function follows the administration of corticotropin, it is due to the inhibition by corticotropin of the production of the thyroid-stimulating hormone of the anterior pituitary lobe. Another hypothetical explanation of the useful role of corticotropin in controlling thyroid storm may assume that such an episode is not equivalent to a sudden severe augmentation of the toxic effects of thyroid hyperfunction, but that it is rather the result of a failure of adrenocortical function that has been overtaxed by the long-continued demands of the thyrotoxic state but which still remains responsive to stimulation by exogenous corticotropin. There has been some evidence presented that in hyperthyroidism the adrenal cortical reserve is in fact diminished,[27] but it remains to be shown through what mechanism such a failing cortex may be stimulated to activity.

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26. (*a*) Hardy, J. D.; Riegel, C., and Erisman, E. P.: Experience with Protein Bound Iodine (PBI): The Effect of ACTH and Cortisone on Thyroid Function, Am. J. M. Sc. **220**:290-292 (Sept.) 1950. (*b*) Hill, S. R., Jr.; Reiss, R. S.; Forsham, P. H., and Thorn, G. W.: The Effect of Adrenocorticotropin and Cortisone on Thyroid Function: Thyroid-Adrenocortical Interrelationship, J. Clin. Endocrinol. **10**:1375-1400 (Nov.) 1950. (*c*) Wolfson, W. Q.; Beierwaltes, W. H.; Robinson, W. D.; Duff, I. F.; Jones, J. R.; Knorpp, C. T., and Eya, M.: Corticogenic Hypothyroidism: Its Regular Occurrence and Clinical Significance During Prolonged Therapeutic Administration of ACTH or Cortisone, J. Lab. & Clin. Med. **36**:1005-1006 (Dec.) 1950.

27. Daughaday, W. H., and Farr, A. L.: Adrenal Cortical Reserve in Severe Hyperthyroidism, J. Clin. Invest. **30**:635 (June) 1951.

D. Sepsis.—The severity of infection in these cases, both in terms of the origin and type of the infectious process and in terms of its clinical course, showed some variations. In Case 20, peritonitis followed maximal operative trauma, and it apparently originated in traumatic (operative) pancreatitis, an essentially noninfectious process—the sum total of intraperitoneal insults was the greatest in this case. Case 21 (diffuse peritonitis following acute sigmoid diverticulitis with perforation) and case 23 (pelvic peritonitis after induced abortion) can be listed next in severity; both patients were dangerously, though not hopelessly, ill. The clinical picture of the infection in Case 22 (pelvic peritonitis due to septic abortion) was unusual only in its being associated with a striking degree of the effects of toxicity on the central nervous system, effects that were also prominent in Cases 21 and 23. Case 24 (spreading peritonitis following instrumental perforation of the urinary bladder) showed no features out of the ordinary. (Because of the intensive antibiotic treatment, the results of bacteriological studies in these cases are not relevant.)

Before attempting to appraise the possible influence of the adrenocorticotropic hormone on the course of the infectious process in these cases, it would seem in order to recall briefly the experimental and clinical evidences of the action of corticotropin in bacterial infection. Reference has already been made to the inhibiting effect of corticotropin on inflammatory reaction of bacterial or nonbacterial origin [28]—the decrease of perivascular exudation and the diminution of the walling-off process owing to the destruction of round cells and to the lack of fibroblastic proliferation. These results of corticotropin action would seem to work counter to the fundamental defensive mechanism and to favor the systemic spread of a local infectious process. It has been shown, on the other hand, that corticotropin also often induces a marked neutrophilic leucocytosis [5a] with a "shift to the left." While this is a variable effect, leucopenia after therapeutic doses is not seen. The systemic manifestations of bacterial infection (as well as many other disease states) i. e., fever, tachycardia, toxicity, exhaustion (fatigue), and pain, have been observed often to be ameliorated by administration of corticotropin.[29] Concerning the immunological mechanisms of the body, no cogent evidence has been presented of a change under corticotropin influence in the titer of circulating antibodies to bacterial antigens.[30]

The experimental evidence in regard to the usefulness of the hormones when administered with therapeutic doses of antibacterial agents in the management of such infections has been inconclusive. Experimentally, corticotropin and cortisone have been demonstrated to be ineffectual and even harmful as sole agents in the treatment of the types of bacterial infection of surgical significance.[31]

28. Dougherty, T. F., and Dougherty, J. H.: Roles of Adrenal Cortical Secretions and Hypersensitivity in Etiology of Mesenchymal Dyscrasias, Anat. Rec. **106**:188-189 (Feb.) 1950. Glaser, J. R.; Berry, J. W.; Loeb, L. H., and Wood, W. B.: The Effects of Cortisone on Acute Bacterial Infections, J. Clin. Invest. **30**:640 (June) 1951. Taubenhaus.[6]

29. Kass, E. H.; Ingbar, S. H., and Finland, M.: Effects of Adrenocorticotropic Hormone in Pneumonia: Clinical, Bacteriological and Serological Studies, Ann. Int. Med. **33**:1081-1098 (Nov.) 1950.

30. Kass, E. H., and Finland, M.: Role of Adrenal Steroids in Infection and Immunity, New England J. Med. **244**:464-470 (March 29) 1951. Mirick, G. S.: The Effect of Adrenocorticotropic Hormone and Cortisone on Antibody Production in Human Beings, J. Clin. Invest. **29**:836 (June) 1950. Fischel.[8b]

31. Robinson, H. J.: Effects of Cortisone on Intradermal Pneumococcal Infections in Rabbits, Federation Proc. **10**:332 (March) 1951.

In discussing the clinical role of corticotropin in bacterial infections, an important distinction must be kept in mind. The hormone has been shown to have remarkable healing powers in pathologic processes that may ultimately be caused by bacterial action (such as rheumatoid arthritis) but in which the noxious effects of the bacteria are due to allergic phenomena or local cellular reactions ("collagen diseases").[1b] In surgical infections, the morbid changes result from direct bacterial activity: proliferation, spread, and toxin production. There is no proof that these bacterial activities are affected by corticotropin or cortisone. These hormones have no bactericidal or bacteriostatic effect.

In the cases summarized above, the hormone was administered always in conjunction with full (and sometimes heroic) doses of antibiotic drugs. The rationale of resorting to the use of corticotropin was twofold: to test the possibility of enhancing the nonspecific reaction to stress (particularly in Cases 20, 21, and 23, in which the patient's "defensive resources" seemed inadequate) and to attempt to ameliorate the systemic manifestations of toxicity (fever, malaise, psychic changes).

The question of whether the hormone in fact exerted a synergistic effect with the antibacterial agents through its nonspecific stimulation of the antistress reaction cannot be answered. There was some suggestive evidence that it may have done so (particularly in Case 21), but far more numerous observations must be gathered before a valid opinion can be formed. On the other hand, clinically at least there was no indication that the hormone interfered with the immunological responses or with the ability of the organism of localizing an infection while appropriate surgical and medicinal therapeutic measures were being carried out. Although the patient in Case 20 died of his diffuse peritonitis, in the tissue sections adequate peritoneal exudation of polymorphonuclear leucocytes and fibrin was noted in response to the infection. The operative trauma and the insult of the supervening acute pancreatitis seemed sufficient cause to account for the failure of the defenses of this patient, and the administration of corticotropin does not seem to have contributed to the outcome.

As regards the alterations that the adminstration of corticotropin brings about in the systemic manifestations of surgical infection, the antipyretic effect[32] of the hormone was frequently noted (in Cases 21 and 23 particularly). The favorable effect on the psychic changes and malaise accompanying severe bacterial infection was observed with some uniformity. Although on the whole these results seem desirable as making for a more agreeable convalescence, they also have disadvantages. The physical signs of intra-abdominal disease are somewhat obscured, and there may be danger of overlooking the deterioration of a disease process masked by the absence of warning signs and by the apparent improvement in the patient's general status.[33]

E. Operative Shock.—The term "operative shock" is used here to denote that type of depression of vital functions (including arterial blood pressure) that accompanies or follows operative trauma and is not primarily or solely due to hemorrhage. In the cases cited this shock did not respond to blood and fluid replacement and

32. Kass, E. H., and Finland, M.: Effect of ACTH on Induced Fever, New England J. Med. **243**:693-695 (Nov. 2) 1950. Kass.[29]

33. Beck, J. C.; Browne, J. S. L.; Johnson, L. G.; Kennedy, B. J., and MacKenzie, D. W.: Occurrence of Peritonitis During ACTH Administration, Canad. M. A. J. **62**:423-426 (May) 1950.

the administration of vasopressor substances, or more precisely, the response to these measures was not evident within a period of time of from 15 minutes to several hours. In Cases 25 and 26, the state of operative shock was of the delayed type, while in the other cases it occurred while the surgical procedures were being carried out.

While by theoretical speculation one may assign an important part to the adrenocortical hormones in the etiology of surgical shock, the factual evidence of such an interrelationship is not strong enough to serve as a basis for the rational use of coticotropin in the treatment of the shock state. There is growing proof, however, that corticotropin has a pressor effect.[34] We looked upon the hormone as a pressor substance in attempting to influence the physiologic alterations associated with shock. As shown by the cases described, the results were inconsistent.

F. Pulmonary Edema.—Three of the instances of this complication took place during surgical operations (Cases 30 to 32), while one occurred after a severe extensive thermal burn (Case 33), and one accompanied terminal uremia (Case 34). Except for Case 33, the hormone was administered as a lifesaving measure in an entirely empirical manner. In Case 33, in which the pulmonary edema may have been the result of a flash burn of the upper air passages, it was theorized, with some basis in experimental facts,[35] that the improvement following the administration of corticotropin was due to a decrease in the exudation of edema fluid brought about by diminished cellular permeability of the pulmonary capillary and by a reduction or disappearance of the inflammatory changes in the bronchiolar, and perhaps also alveolar, epithelium. Even if these changes follow corticotropin administration in burn injury (and there is strong evidence that at least the effect on capillary permeability does not take place),[36] they obviously could not have been responsible for the favorable results in other cases, whose pulmonary edema had been caused by increased pulmonary venous pressure. Thus the improvement in acute pulmonary edema observed in the foregoing cases cannot be explained in a physiologically sound way.

G. Hypersensitivity States.—The profound effect of corticotropin and cortisone on allergic reactions has been demonstrated in a large volume of experimental and clinical work.[1c] Hypersensitivity is markedly diminished or abolished by the hormones to a wide variety of antigens, probably through an altered reaction in the target tissue to the antigen-antibody union. In a group of patients manifesting hypersensitivity reactions of surgical interest, corticotropin and/or cortisone was administered in total doses of from 25 to 400 mg. The allergenic factors were as follows: blood transfusion (two cases), scopolamine hydrobromide as preanesthetic medication (one case), chloramphenicol (chloromycetin®) (one case),

34. Ransohoff, W.; Brust, A. A.; Chambers, W. N.; Shapiro, A. P.; Reiser, M. F.; Loube, S. D.; Mirsky, I. A., and Ferris, E. D.: The Effect of Sodium Intake on the Action of ACTH in Uncomplicated Essential Hypertension, J. Clin. Invest. **29**:839-840 (June) 1950. Kass.[29]

35. Hyman, C., and Chambers, R.: Effect of Adrenal Cortical Compounds on Edema Formation of Frogs' Hind Limbs, Endocrinology **32**:310-318 (April) 1943. Seifter, J.; Baeder, D. H., and Dervinis, A.: Alteration in Permeability of Some Membranes by Hyaluronidase and Inhibition of This Effect by Steroids, Proc. Soc. Exper. Biol. & Med. **72**:136-141 (Oct.) 1949.

36. Cope, O.; Graham, J. B.; Mixter, C., Jr., and Ball, M. R.: Threshold of Thermal Trauma and Influence of Adrenal Cortical and Posterior Pituitary Extracts on the Capillary and Chemical Changes: Experimental Study, Arch. Surg. **59**:1015-1030 (Nov.) 1949.

tetanus antitoxin (two cases), penicillin (two cases), hexylchloro-*m*-cresol as skin antiseptic (one case), and medicinal soft soap with hexachlorophene (one case). Except in one case of penicillin sensitivity and one case of serum sickness due to tetanus antitoxin, prompt relief was obtained. The effect of these hormones in the prevention and treatment of transfusion reactions seems worthy of further exploration. One of us (R. R. M.) has found in unpublished work that the Rh antibody titer can also be lowered by the administration of corticotropin and cortisone.

H. Postoperative Intravenous Clotting.—The effect of corticotropin and cortisone on the blood-clotting mechanism is not well understood. From the few observations reported,[37] the following hypothetical interrelationship between the cortical hormones and blood coagulation may be formulated. The coagulation factor principally affected by cortisone-like hormones is heparin. By the destruction of mast cells (which are the seat of the formation of heparin) these hormones may either increase or decrease the level of circulating heparin. The destruction of mast cells in general liberates heparin, but the level of the circulating anticoagulation factor will depend on the existing store of mast cells in the organism and its rate of regeneration in relation to its rate of destruction.

From the practical point of view, the danger of hyperheparinemia (which is usually associated with hypoprothrombinemia) and the resultant bleeding tendency under the influence of corticotropin or cortisone given in customary therapeutic doses in a patient with otherwise normal blood-clotting mechanism seems to be of little importance. The retardation of blood coagulation under these circumstances is slight and temporary. We have not encountered a tendency to bleeding in the patients observed in this study. However, when large doses of corticotropin or cortisone are administered over prolonged periods of time and then abruptly stopped, adenohypophysial and cortical function, depressed by the exogenous hormones, may be insufficient to cause the freeing of an adequate amount of heparin from the depleted mast cells to maintain a normal blood "antithrombin" level. Such an event may increase the coagulability of the blood and lead to spontaneous intravascular clotting. In one of our cases discussed in an earlier paragraph (Case 7), there was evidence that this phenomenon may have taken place.

In 13 cases of venous clotting, 9 of which were postoperative, 2 primary, 1 puerperal, and 1 chemical, the effects of corticotropin were studied as sole therapeutic agents in doses of 60 to 100 mg. daily for 4 to 10 days. The cases were diagnosed by the usual clinical criteria. Significant reduction of the blood prothrombin level was noted in nine cases. Protamin titration was carried out in three cases and showed elevated heparin levels. There seemed to be clinical improvement in all cases, in one case of rather dramatic promptness. Owing to the existence of other methods of treatment for venous clotting which, although not ideal, give excellent results and are safer and easier of application, these observations have only a theoretical interest.

37. Smith, R. W.; Margulis, R. R.; Brennan, M. J., and Monto, R. W.: The Influence of ACTH and Cortisone on Certain Factors of Blood Coagulation, Science **112**:295-297 (Sept. 15) 1950. Margulis, R. R.: Blood Coagulation as Affected by ACTH and Surgical Stress, in Surgical Forum: Proceedings of the Forum Sessions, Thirty-Sixth Clinical Congress of the American College of Surgeons, Boston, October, 1950, Philadelphia, W. B. Saunders Company, 1951, pp. 507-516. Cosgriff, S. W.; Diefenbach, A. F., and Vogt, W.: Hypercoagulability of the Blood Associated with ACTH and Cortisone Therapy, Am. J. Med. **9**:752-756 (Dec.) 1950.

SUMMARY AND CONCLUSIONS

1. In the doses used, corticotropin (60 to 120 mg. daily for 5 to 10 days) and cortisone (100 to 130 mg. daily for 5 to 10 days) produced few untoward effects, and all of these were minor.

No significant disturbances of the water and electrolyte metabolism and of wound healing were noted. The concealment of physical signs (temperature and pulse elevation, reflex muscle spasm, tenderness) and symptoms (pain) by the action of the hormones was noted but was not of a degree to interfere seriously with the diagnosis or evaluation of the progress of intra-abdominal disease.

Intravascular clotting is a potential complication of postoperative corticotropin and cortisone therapy, particularly if the dosage is large, the administration prolonged, and the discontinuation abrupt.

The presence of chronic peptic ulcer and probably also of other chronic ulcerative lesions of the gastrointestinal tract is a contraindication to the use of corticotropin and cortisone.[38] In patients with diabetes mellitus and hypersensitive nephropathy, the adminstration of these hormones demands great caution.

2. Until much more information is gathered, no valid statement can be made regarding the effectiveness of corticotropin and cortisone in augmenting adrenocortical function against nonspecific stress, i. e., during the convalescence of impaired-risk patients and in the treatment of patients in a state of physiologic exhaustion.

In the absence of reliable quantitative tests of adrenocortical function for the correlation of the clinical status and of the cortical reserve of the patient, the use of the hormones is entirely empirical and should be avoided except for the purpose of gathering, under appropriate conditions, further knowledge of the problems involved.

3. Evidence was obtained that in postoperative hypotensive oliguria corticotropin has a corrective effect on the renal function. Corticotropin and cortisone were likewise found effective in the treatment of some allergic states that have some interest for the surgeon.

In the management of thyroid crisis the cautious use of corticotropin seems justified although its mode of action is not well understood.

In the treatment of venous clotting, corticotropin and cortisone, though rather effective, show some disadvantages and no advantages over the established anticoagulant methods.

In the therapy of postoperative infection the place of corticotropin and cortisone seems to be highly restricted. One may resort to the utilization of their effects on the systemic manifestations of toxicity in instances of infection in which these are unusually severe. However, their application must always be secondary to specific antibacterial measures.

In the management of lower nephron nephrosis, corticotropin and cortisone were of little or no value. In the cases of operative shock and acute pulmonary edema, the observed effects of corticotropin and cortisone were equivocal.

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38. Habif, D. V.; Hare, C. C., and Glaser, G. H.: Perforated Duodenal Ulcer Associated with Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **144**:996 (Nov. 18) 1950.

ABSTRACT OF DISCUSSION

DR. DAVID M. HUME, Boston: I have been interested in listening to Dr. Szilagyi's paper. We have treated 75 surgical patients with corticotropin and cortisone in the Peter Bent Brigham Hospital in Boston. Our results closely parallel those you have just heard.

We were very much interested in its use postoperatively and preoperatively in patients who were poor surgical risks, or who seemed to be doing poorly. It is almost impossible to tell which patients are going to need this treatment preoperatively in the absence of readily demonstrable corticotropin deficiency. Therefore, we have treated the patients preoperatively as usual, and, if the patients seem to be rather poor candidates for surgery at the end of the time, we administer corticotropin or cortisone.

(Slide) This is a 53-year-old patient who had an epidermoid carcinoma of the anus. We planned to do a resection of the rectum, sigmoid, and anus and a total hysterectomy. The patient did not do well almost from the onset, the blood pressure coming down to zero and staying there during much of the operation. Therefore we did not do the entire contemplated operation but ended by doing the colostomy and hysterectomy and turning in the rectal stumps.

During the postoperative phase the patient's blood pressure returned to normal, and she made a fairly good recovery from the operation.

Three weeks later we performed the resection of the rectal stump, which was a very simple surgical procedure. Ten minutes after the operation was started, the blood pressure was zero in spite of the fact that she had lost very little blood. The operation took 20 minutes, and 30 minutes after the end of the operation the patient had no measurable blood pressure. The pressure then gradually came back, but during the night the patient frequently slipped into lapses during which there was no blood pressure reading obtainable at all, and by the next morning she looked very poorly.

During the 24 hours in the postoperative period, she excreted a total of 80 cc. of urine, and at that time the eosinophile count was 80, and the blood pressure was zero. We did a basal metabolic test and the reading was +6; we had no reason to suspect that the patient would not respond well to the operation.

We began treatment with corticotropin in the postoperative period, and she continued excellently and recovered uneventfully.

Then we planned to do a bilateral radical dissection of the groin on this patient. We treated her with corticotropin for seven days, and she responded well, with a good fall in the eosinophile count. At the end of the time her eosinophile count was 1,000. We changed to cortisone and treated her for two days preoperatively with cortisone, got a good response in eosinophiles, maintaining her eosinophiles during the operation.

During the third procedure, by far the bloodiest of the three, her blood pressure was perfectly normal, and her recovery was perfectly normal. Her urinary output after the operation was 1,745 cc.

(Slide) This illustrates a similar response in a patient also tested with both corticotropin and epinephrine preoperatively, who responded normally. This patient had spinal anesthesia. In the postoperative period she became hypotensive, with a blood pressure of zero for almost three hours. During this time she received blood, and at the end of the time her hematocrit reading was 45. She had not lost any undue amount of blood. She also received the usual stimulus during this time, without any effect on the blood pressure.

At this point we began the intravenous administration of 25 mg. of corticotropin, which is a large dose when given by this means, giving it to her in a constant drip. Within one hour her blood pressure had returned to a normal level, and it remained there during her postoperative course. Her recovery was uneventful.

We also have been interested in using corticotropin and cortisone in several specific surgical cases. We tried it for acute pancreatitis in eight patients, and it has no specfic beneficial effect in this disease in our hands.

We also tried it in two patients with acute periostitis, and it had no beneficial effect. We tried it in 10 patients with acute bursitis, 8 of whom had failed to respond to the usual methods of treatment. The response in this disease was very striking. The patients all became better within a period of 24 hours and were all asymptomatic within 24 to 72 hours.

We now treat the disease by giving the patient corticotropin intravenously, 30 mg. a day in a constant drip, having put a polyethylene catheter in the patient's vein, and discharge him 24 hours after he becomes asymptomatic.

The treatment in chronic bursitis is very disappointing. We have also tried using corticotropin in cases of acute tenosynovitis of noninfectious origin, and the result is almost as striking as in bursitis.

We have also tried it in thrombophlebitis. Our results were the same as Dr. Szilagyi's. We got very good results in the 10 patients we treated. Eight of the patients had no other treatment than corticotropin. As Dr. Szilagyi does, we feel that one should not use this as the only agent to treat this disease, but should add it in cases which fail to respond to hydration, the administration of bishydroxycoumarin (dicumarol®), and other like measures. We used it in one patient, and he made a very good response.

In no case is it a substitute for general methods of surgical care.

(Slide) I should like to list the contraindications to its use, because I think they are most important. We feel that in surgical infections it is definitely a dangerous agent. We have had one patient with a burn who got a septicemia from infection in the burned area following the use of corticotropin. We have had two patients who have had large abdominal abscesses following the use of corticotropin. We feel that even in the presence of antibiotics it is dangerous to use it with severe infections.

We have not felt it was contraindicated specifically in healing surgical wounds, but one must use some care in its use. We have also had occasion to regret its use in patients with active peptic ulcers. We have used it in burn patients, but we do not feel it is in any way a substitute for any of the usual methods of treating burns, including that of the local treatment of burns.

We have felt it was of some value in the early treatment, from 7 to 14 days, and we prefer to begin the treatment with cortisone rather than corticotropin, because a number of patients who die in the early postburn period show pathological changes in the adrenal cortex.

We do not think it is wise to flail the patient's adrenalcorticotropic hormone with added amounts of corticotropin at this time. We use cortisone and push back the patient's own corticotropin and then begin the corticotropin therapy after three or four days, and always discontinue it at the end of two weeks.

Dr. Geza DeTakats, Chicago: Attention should be called to the fact that the incidence of thromboembolic phenomena following the use of corticotropin or cortisone in different disorders is around 10%.

We ourselves have been interested in this problem for some time and find that the normal clotting mechanism responds with a shortening and, after that, a lengthening of the clotting time. However, an exhausted clotting mechanism can be pushed into massive thrombosis.

I should like to make the point that for patients who are already depleted and exhausted and who have already shown a massive corticotropin response as a result of surgical trauma, treatment with cortisone or corticotropin constitutes a real hazard, particularly in regard to thromboembolism.

Dr. D. Emerick Szilagyi, Detroit: The effect of corticotropin on the clotting mechanism is exceedingly complex and has not been worked out very well. It is fundamentally a function of the reserve of mast cells of the body that are the seat of heparin formation. This, when exhausted, may fail to continue to produce heparin, and thus the patient may have a clotting mechanism which is abnormal, and spontaneous clotting may occur.

I should like to point out one other factor which I think stands out when one compares the experimental work and the clinical results concerning wound healing: There is very convincing evidence experimentally that corticotropin is a destructive force in wound healing. We have always been looking with a great deal of apprehension at the progress of the patients whom we studied postoperatively. To our great surprise, we have not found wound incidence, and apparently the gastrointestinal anastomosis lines remained well healed.

In one section that I showed there was not adequate response in the suture line in the healing process. It is rather mysterious to explain how these people, nevertheless, maintain a firm anastomotic line. In that particular instance, during the postmortem examination we actually tested the strength of the line, and it did not part without applying great force.

QUANTITATIVE STUDIES ON EFFECT OF GASTROJEJUNOSTOMY ON GASTRIC SECRETION

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THE DATA secured in the present investigation establish the surprising fact that certain types of gastroenterostomy in dogs produce a profound stimulation of the secretion of gastric juice by the body and fundus of the stomach. These studies were prompted by the previous observation, in this laboratory, that the Mann-Williamson procedure for the production of experimental stoma ulcers regularly causes a hypersecretion of acid gastric juice.[1] The development in this laboratory of a method for the quantitative collection of gastric juice from isolated stomach pouches of various types for long periods has made it possible to restudy the physiology of gastric secretion and to estimate the relative importance of various stimulating mechanisms on the total amount of gastric secretion produced in a measured interval of time.[2] With use of these methods it has been determined that 40% of the total output of gastric juice in normal dogs is dependent upon the nervous, or vagus, phase of gastric secretion; about 40% on the humoral, or gastrin, phase, and 10% or less on the intestinal phase of gastric secretion. The secretion of gastric juice aroused by the presence of food in the stomach is mediated exclusively by the antrum, which functions as an endocrine organ for the production of the gastric secretory hormone, gastrin.[3] The production and release of gastrin from the antrum of the stomach is due to contact of the antrum mucosa with food or some of its digestion products. It may also be profoundly stimulated by distention within physiological limits. The application of food plus distention seems to be a more potent stimulus to the antrum than either factor alone. Transplantation of the antrum of the stomach into the colon as a diverticulum so that the

From the Department of Surgery of the University of Chicago.

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antrum mucosa is exposed to fecal material produces a profound and long-sustained hyperfunction of the antrum with a resultant hypersecretion of gastric juice and ulcer formation.[4] On the other hand, the application of acid solutions to the antrum mucosa inhibits the production and release of gastrin and, as a consequence, stops the secretion of gastric juice due to the presence of food in the stomach.

There is now abundant evidence indicating that a hypersecretion of gastric juice is regularly found in patients with duodenal ulcers, both in the fasting stomach and as a result of stimulation by food, alcohol, or histamine.[5] This hypersecretion is comparable in extent to that which has been found to produce duodenal ulcers and gastrojejunal ulcers in experimental animals.[6] Success in the treatment of duodenal ulcers by surgical procedures has been roughly proportionate to the degree to which these procedures abolish the hypersecretion of gastric juice in these patients. Gastrojejunostomy has been extensively used since its introduction by Woelfler, in 1881, and von Hacker, in 1885, and there can be no doubt that it exerts a powerful curative effect on duodenal ulcers. The mechanism of this action has remained undetermined, although a subject for much speculation. With the development of quantitative methods for studying gastric secretion, it seemed advisable to examine again by precise methods the effect of this common operation on the secretion of gastric juice.

EXPERIMENTAL METHODS

Mongrel dogs were used for the experiments, and all operations were performed with the animals under ether anesthesia and with the usual aseptic precautions. Three types of preparation were made, namely, Pavlov pouches, Heidenhain pouches, and Heidenhain pouches prepared from the fundus of the stomach in animals in which the antrum had been previously extirpated.

Method of Collection.—Following a 10 day postoperative recovery period, quantitative 24-hour collections of gastric juice from the accessory stomach pouches were secured by means of nylon plastic cannulas inserted into the pouch at the time of operation. These were attached to rubber bladders as previously described from this laboratory. The total amount of gastric juice secreted in each 24 hours was collected every day, its volume measured, and the free acid concentration titrated with Toepfer's reagent. After the pouch had started secreting at a more or less constant rate, the daily secretion of each dog was determined for at least 24 days so that the secretory activity of each preparation was well known. After this control period a gastrojejunostomy was performed and the gastric juice collected daily for a period of 21 to 39 days, when the anastomosis was taken down and collections again made for a second control period of comparable extent.

Surgical Technique.—Both anterior and posterior gastrojejunostomies were made with the jejunum about 10 cm. distal to the ligament of Treitz. The anastomosis was made just above the greater curvature of the stomach, and the jejunum was applied either in an antiperistaltic or an isoperistaltic direction. The position of the stoma was in one of two places, (*a*) in the lower body or (*b*) in the antrum (Charts 1 and 2). In some animals the two positions were used in sequence to compare the effects of each operation in the same animal. Rubber-covered gastroenterostomy clamps were employed, and the suture material was tannic acid surgical gut on an atraumatic needle. The diameter of the stoma was approximately 2.5 to 3 cm.

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Expression of Results.—The means of volumes are expressed in cubic centimeters. The means of free hydrochloric acid concentration are expressed in clinical units. The means of free hydrochloric acid output per 24-hour period are expressed in milliequivalents. The product of the volume in liters by the free hydrochloric acid concentration expressed in clinical units gives the amount of free hydrochloric acid in terms of milliequivalents. The standard error was calculated in all the figures.

EXPERIMENTAL RESULTS

Series A—The Effect of Gastrojejunostomy with the Stoma in the Body of the Stomach on Gastric Secretion.—The data of these experiments are summarized in Table 1 and a representative experiment graphically illustrated in Chart 1.

Dog 413—Heidenhain Accessory Stomach Pouch with the Vagus Nerves to the Pouch Divided: During a preliminary control period, 24 daily collections of

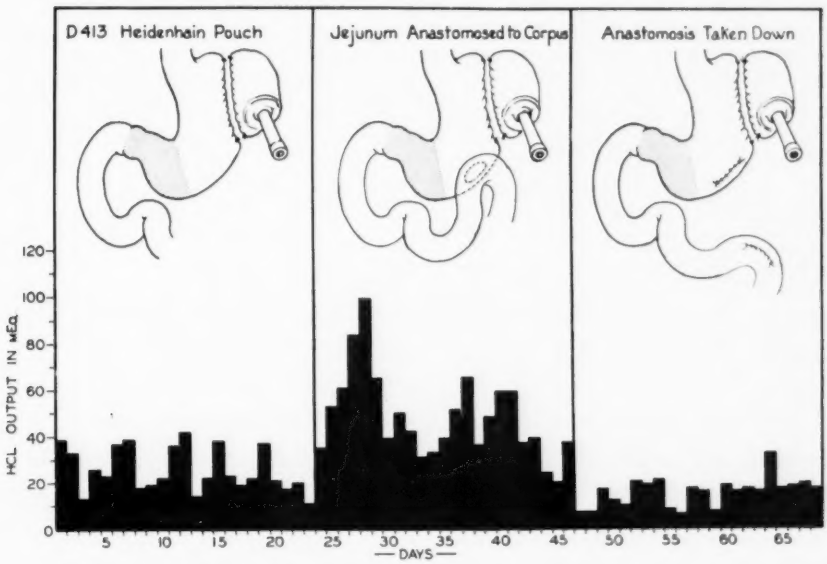

Chart 1.—Stimulating effect of gastrojejunostomy on the output of hydrochloric acid from a vagus-denervated Heidenhain pouch. The daily output of acid from the pouch is expressed in milliequivalents, obtained by multiplying the volume secreted in a 24-hour period, expressed in liters, by the free acid concentration, expressed in clinical units.

gastric juice yielded an average of 228 cc., with a free acid concentration of 108 clinical units and a calculated average daily output of 25 mEq. of free hydrochloric acid. A gastrojejunostomy was then made with the stoma in the body of the stomach. Twenty-five daily collections of secretion from the isolated pouch revealed an increase in the average 24-hour volume to 381 cc., with an average free acid concentration of 121 clinical units and a calculated output of 46 mEq. of free hydrochloric acid, or an increase of 84% over the control level. The gastrojejunostomy was then taken down, and during this second control period, of 50 days, the average secretion of gastric juice decreased to 158 cc. per day, with a free acid concentration of 96 clinical units and a calculated free acid output of 15 mEq. per day.

This experiment was repeated in the same animal, except that a posterior gastrojejunostomy was made instead of an anterior anastomosis, with the result summarized in Table 1. It is again evident that the gastrojejunostomy produced a significant increase in gastric secretion.

Dog 382—Pavlov Pouch: During the preliminary control period, of 31 days, an average volume of 553 cc. of gastric juice was secreted daily, with an average free acid concentration of 144 clinical units and a calculated free acid output of 80 mEq. per day. A gastrojejunostomy was then constructed with the stoma in the body of the stomach. Twenty-three 24-hour collections of gastric secretion revealed an average increase in the volume to 917 cc., an average increase in the free acid concentration to 147 clinical units, and an increase in the output of free hydrochloric acid to 135 mEq., or an increase of 67%. The gastrojejunostomy was then taken down and gastric secretion collected for a second control period, of 30 days.

TABLE 1.—*Effect on Gastric Secretion of Gastroenterostomy Placed in Body of Stomach*

	Control						Gastroenterostomy						Control					
Preparation	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	±	S. E.	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	±	S. E.	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	±	S. E.
Heidenhain dog 413	24	228	108	25	±	1.9	25	381	121	46	±	3.7	50	158	96	15	±	2.9
Dog 413, experiment repeated	50	158	96	15	±	2.9	32	285	125	36	±	2.5	28	147	98	14	±	1.0
Pavlov dog 382	31	553	144	80	±	5.4	23	917	147	135	±	7.5	30	742	148	110	±	4.9
Pavlov dog 449	41	146	128	19	±	0.76	30	195	128	25	±	1.94	29	176	125	22	±	2.2
Dog 449, experiment repeated	29	176	125	22	±	2.2	28	242	135	33	±	1.9	26	215	129	28	±	1.6
Heidenhain dog 453	29	284	130	37	±	2.7	28	404	130	52	±	1.7	..	....	....	..		....
Heidenhain dog 454	36	199	122	24	±	1.5	21	277	134	37	±	2.4	..	....	....	..		....

The 24-hour volume dropped to 740 cc. with an average free acid concentration of 148 clinical units, and a calculated free hydrochloric acid output of 110 mEq.

Dog 449—Pavlov Pouch: The preliminary control period of 41 daily collections of gastric juice revealed an average volume of 146 cc. with an average free acid concentration of 128 clinical units, and a calculated free hydrochloric acid output of 19 mEq. Gastrojejunostomy was then performed with the stoma in the body of the stomach, and 30 daily collections of gastric juice were made. The average volume of secretion increased to 195 cc. per day, with an average free acid concentration of 128 clinical units and a calculated free acid output of 25 mEq. per day, or an increase of 31%. The gastroenterostomy was then taken down, and 29 daily collections of gastric secretion were made. The average volume decreased to 176 cc. per day, with a free acid concentration of 125 clinical units and a calculated free hydrochloric acid output of 22 mEq.

The experiment was repeated with the same animal, and again a significant increase in gastric secretion from the isolated stomach pouch followed the gastrojejunostomy. The details are summarized in Table 1.

Dog 453—Heidenhain Pouch with the Vagus Nerve Supply to the Isolated Pouch Divided: This animal had previously had a gastrojejunostomy with the stoma in the antrum of the stomach. The anastomosis in this region produced a slight and probably insignificant reduction in secretion (Series B, Table 2). The gastroenterostomy was then taken down, and during a control period of 29 days an average daily volume of 284 cc. of gastric juice was secreted, with an average free acid concentration of 130 clinical units and a calculated free acid output of 37 mEq. per day. A gastrojejunostomy was then performed with the stoma in the body of the stomach. Twenty-eight daily collections of gastric juice were then secured, which revealed an average increase in volume to 404 cc. per day, with a free acid concentration of 130 clinical units and a calculated free hydrochloric acid output of 52 mEq., or an increase of 40%.

Dog 454—Heidenhain Pouch with the Vagus Innervation to the Pouch Divided: In this animal also a gastrojejunostomy with the stoma in the antrum produced a slight reduction in both the volume and the hydrochloric acid output of the gastric juice (Table 2). The gastrojejunostomy was then taken down and thirty-six

TABLE 2.—*Effect on Gastric Secretion of Gastroenterostomy Placed in the Antrum*

	Control					Gastroenterostomy					Control				
Preparation	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	S. E.	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	S. E.	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	S. E.
Heidenhain dog 453	45	279	136	38	± 2.4	33	264	121	32	± 2.4	29	284	130	37	± 2.7
Heidenhain dog 454	50	274	130	36	± 2.2	22	269	131	35	± 2.8	36	199	122	24	± 1.5
Heidenhain dog 413	28	147	98	14	± 1.0	39	144	94	13	± 1.1	..	...	...	..	...

24-hour collections of gastric juice were made. This revealed an average volume of 199 cc., with an average free acid concentration of 122 clinical units and a calculated free hydrochloric acid output of 24 mEq. A gastrojejunostomy was then made with the stoma in the body of the stomach and 21 daily collections of gastric juice secured. The average daily volume increased to 277 cc., with a free acid concentration of 134 clinical units and a calculated free hydrochloric acid output of 37 mEq., or an increase of 54%.

Series B—The Effect of Gastrojejunostomy with the Stoma in the Antrum of the Stomach on Gastric Secretion.—The data in this series of experiments are summarized in Table 2 and a representative experiment is graphically illustrated in Chart 2.

Dog 453—Heidenhain Pouch with the Vagus Nerve Supply to the Pouch Divided: During the control period, forty-five 24-hour collections of gastric juice were made, which revealed an average daily secretion of 279 cc., with a free acid concentration of 136 clinical units and a calculated average free hydrochloric acid output of 38 mEq. A gastrojejunostomy was then made with the stoma in the antrum of the stomach. Thirty-three daily collections of gastric juice revealed an average 24-hour output of 264 cc., with a free acid concentration of 121 clinical units and a free hydrochloric acid output of 32 mEq. In contrast to the experiments

in which the gastrojejunostomy was made in the body of the stomach, in this case a decrease in gastric secretion occurred when the gastrojejunostomy was placed in the antrum of the stomach. The gastrojejunostomy was then taken down, and 29 daily collections of gastric juice were made. The average volume increased to 284 cc., with a free acid concentration of 130 clinical units and a calculated free hydrochloric acid output of 37 mEq., almost exactly the same as was obtained during the first control period.

Dog 454—Heidenhain Pouch with the Vagus Nerve Supply to the Pouch Divided: Fifty daily collections of gastric juice were made during the control period, and these revealed an average output of 274 cc., with a free acid concentration of 130 clinical units and a calculated free acid output of 36 mEq. A gastrojejunostomy

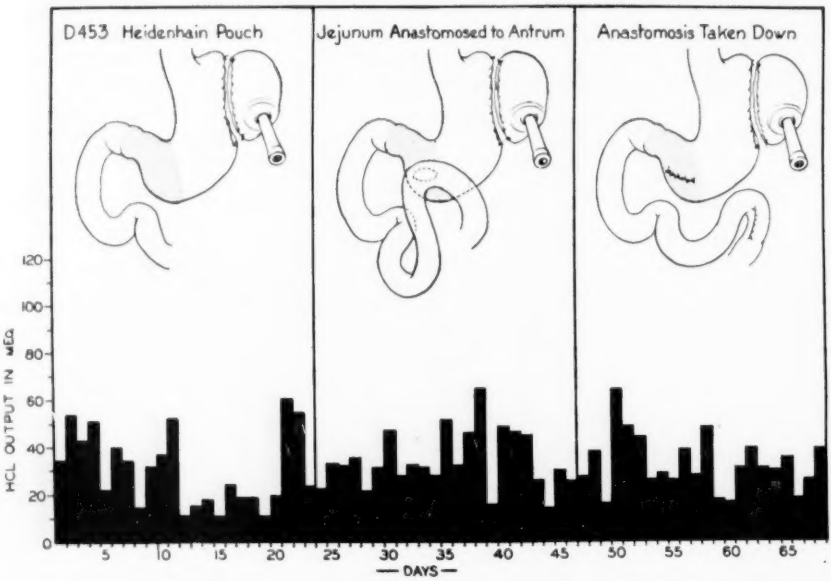

Chart 2.—Negative effect of gastrojejunostomy on secretion of gastric juice by a Heidenhain pouch when the anastomosis is made in the antrum of the stomach.

was then made with the stoma in the antrum and 22 daily collections of gastric juice secured. The average volume decreased to 269 cc., with an average free acid concentration of 131 clinical units and a free hydrochloric acid output of 35 mEq. The gastroenterostomy was then taken down and 36 daily collections of gastric juice secured. The average volume decreased to 199 cc. with a free acid concentration of 122 clinical units and a free hydrochloric acid output of 24 mEq. In this case, the gastroenterostomy with the stoma in the antrum of the stomach produced no significant effect on gastric secretion, but for some reason when the gastroenterostomy was taken down a definite fall in hydrochloric acid output occurred. In this animal a gastroenterostomy with the stoma in the body of the stomach produced a marked increase in gastric secretion, as may be seen in Table 1.

Dog 413—Heidenhain Pouch with the Vagus Nerves to the Pouch Divided: During a previous experiment with this animal, both an anterior and a posterior gastrojejunostomy with the stoma in the body of the stomach produced a definite increase in gastric secretion (Series A). During the control period of 28 daily collections of gastric juice, an average daily volume of 147 cc. was secured, with a free hydrochloric acid concentration of 98 clinical units and a calculated acid output of 14 mEq. A gastrojejunostomy was then performed with the stoma in the antrum, and 39 daily collections of gastric juice were secured. The average volume of secretion was 144 cc., with a free acid concentration of 94 clinical units, and a free hydrochloric acid output of 13 mEq.

Series C—The Effect of Gastrojejunostomy with the Stoma in the Body of the Stomach on Gastric Secretion After Previous Extirpation of the Antrum.—The data

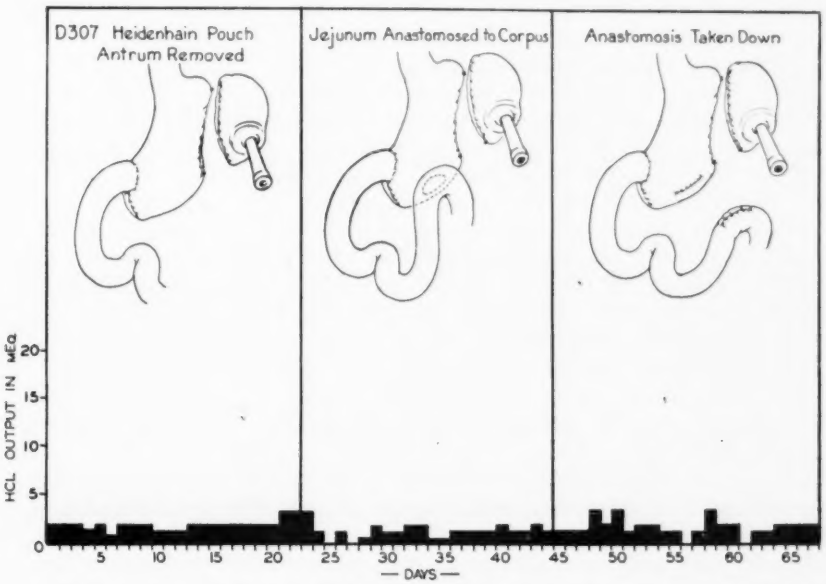

Chart 3.—Negative effect of gastroenterostomy on the output of acid from a Heidenhain pouch when a gastroenterostomy is made after previous extirpation of the antrum.

in this series of experiments are summarized in Table 3 and a representative experiment graphically illustrated in Chart 3.

Dog 307—Heidenhain Pouch with Extirpation of the Antrum of the Stomach and Reestablishment of Intestinal Continuity by Gastroduodenostomy: During the control period, 24 daily collections of gastric juice were made, revealing an average volume of 44 cc., with a free acid concentration of 38 clinical units and a calculated free acid output of 1.7 mEq. per day. A gastrojejunostomy was then made with the stoma in the body of the stomach and 28 daily collections of gastric juice secured. The average daily volume was again 38 cc., with a free acid concentration of 31 clinical units and a calculated free acid output of 1.2 mEq. per day. The gastroenterostomy was then taken down and 30 daily collections of gastric juice secured.

The average volume was 41 cc., with a free acid concentration of 28 clinical units and a calculated free acid output of 1.1 mEq. per day. This experiment brings out the fact that gastrojejunostomy with a stoma in the body of the stomach does not increase gastric secretion if the antrum has been previously removed.

Dog 331—Heidenhain Pouch with Extirpation of the Antrum of the Stomach and Reestablishment of Intestinal Continuity by Gastroduodenostomy: During the control period, 28 daily collections of gastric juice were made, revealing an average output of 152 cc. with a free acid concentration of 42 clinical units, and a calculated free acid output of 6.4 mEq. A gastrojejunostomy was then performed with the stoma in the body of the stomach and 31 daily collections of gastric juice secured. The average output decreased to 105 cc. per day, with a free hydrochloric acid concentration of 64 clinical units and a free acid output of 6.8 mEq. In this experiment, also, gastrojejunostomy failed to increase gastric secretion after removal of the antrum.

TABLE 3.—*Effect on Gastric Secretion of Gastroenterostomy in the Presence of Nonfunctioning Antrum*

	Control					Gastroenterostomy					Control				
Preparation	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	S. E.	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	S. E.	Days	Volume, Cc.	Free Acid, Clin. U.	HCl, mEq.	S. E.
Heidenhain dog 307	24	44	38	1.7	± 0.1	28	38	31	1.2	± 0.1	30	41	28	1.1	± 0.2
Heidenhain dog 331	28	152	42	6.4	± 0.6	31	105	64	6.8	± 0.4	..	...	...	...	...

COMMENT

The data obtained in these experiments are consistent and establish the fact that gastroenterostomy produces a sustained and marked increase in the secretion of acid gastric juice by the body and fundus of the stomach. The increase in the output of free hydrochloric acid varied between 31 and 140% of the initial value. This increase in secretion occurred with both an anterior and a posterior gastrojejunostomy, provided the stoma was constructed in the body of the stomach. The increase in acid output was due primarily to an increase in the volume of gastric juice secreted, since the concentration of free acid was not significantly changed.

The mechanism by which a gastrojejunostomy stimulates the secretion of gastric juice is not entirely clear, but several significant points have been established. In the first place, the increase in secretion took place from an isolated pouch of the body and fundus of the stomach that was free from vagus innervation. The stimulation is consequently not of nervous origin. The finding that a similar type of gastroenterostomy does not stimulate gastric secretion if the antrum of the stomach has been removed suggests that the humoral agent responsible for the stimulation has its origin in the antrum mucosa and may be the gastrin hypothesized by Edkins. The fact that the major part of the body and fundus of the stomach, as well as the upper intestinal tract, is still present indicates that a humoral agent from this source is not involved. The question arises, How does a gastroenterostomy with a stoma

in the body of the stomach increase the output of gastrin from the antrum? Some light is thrown on this problem by the observation that gastrojejunostomy does not increase gastric secretion if the stoma is placed in the antrum of the stomach. Thus in Series B, with the antrum as the site of the anastomosis, gastroenterostomy produced little or no difference in either the volume of gastric juice secreted or its free acid concentration. To verify the validity of this finding, the same experiment of gastrojejunostomy but with the stoma in the body of the stomach was repeated in the same animal, in which a previous gastrojejunostomy in the antrum had been ineffective. A marked increase in secretion occurred, indicating that the site of the stoma was a significant factor in the experiment and not an unusual reaction on the part of the experimental animal. The reverse experiment was also performed, first with a gastroenterostomy with the stoma in the antrum, yielding no significant increase in secretion. Later this anastomosis was taken down, and after a control period a gastroenterostomy in the same animal, but with the stoma in the body of the stomach, was performed and a striking increase in secretion occurred.

Some recent observations on the physiology of gastrin release from the antrum are helpful in a further analysis of this problem. According to Babkin,[7] Sokolov, working in Pavlov's laboratory, discovered that in the dog the introduction of 0.5% hydrochloric acid solution into the stomach markedly diminished the secretion of gastric juice from a Pavlov pouch. Subsequently Wilhelmj, O'Brien, and Hill[8] found that acid can inhibit the gastric phase of secretion by showing that the introduction of acid solution into the isolated stomach pouch inhibits the secretion of gastric juice. Oberhelman, Woodward, Zubiran, and Dragstedt[9] found that the usual profound stimulation of gastric secretion produced by transplantation of the antrum into the colon was lessened if the antrum plus a small portion of the acid-secreting body was used for the transplant. When the acid-secreting body mucosa was removed from the transplant, augmentation of gastric secretion from the isolated stomach pouch occurred. Furthermore, these authors observed that the application of acid to an isolated antrum pouch can inhibit the release of gastrin from the antrum, occasioned by either distention or the application of food. Acid applied to the antrum mucosa also inhibited the spontaneous secretion of gastric juice from a Pavlov or Heidenhain pouch.

A tentative explanation for the stimulating effect of gastroenterostomy on gastric secretion may be formulated as follows. Under normal conditions the secretion of gastric juice from the vagus-denervated Heidenhain pouch is primarily due to the release of gastrin from the antrum of the stomach as a result of the presence of food in the stomach. As the secretion of gastric juice in the main stomach gradually overcomes the neutralizing or buffering action of the food, the gastric content becomes appreciably acid in reaction and inhibition of antrum function comes into play. It is possible that a gastrojejunostomy with the stoma in the body of the stomach either decreases this acid inhibition of antrum function by draining away the acid secretions of the body and fundus before they come in contact with the antrum mucosa or decreases the acidity of the gastric content as a result of reflux

7. Babkin, B. P.: Secretory Mechanism of the Digestive Glands, Ed. 2, New York, Paul B. Hoeber, Inc., 1950, p. 642.

8. Wilhelmj, C. M.; O'Brien, F. T., and Hill, F. C.: Am. J. Physiol. **115**:429, 1936.

9. Oberhelman, H. A., Jr.; Woodward, E. R.; Zubiran, J. M., and Dragstedt, L. R.: Am. J. Physiol., to be published.

of alkaline duodenal juices through the stoma. The observation that gastroenterostomy with the stoma in the antrum fails to produce hypersecretion suggests that a reflux of duodenal content into the stomach is of less significance, since this should be approximately the same irrespective of the site of the stoma.

An effective physiological mechanism for diminishing the secretion of acid is the increase in the acidity of the gastric content coming down into contact with the antrum mucosa. Contrariwise, a lessened acidity of the gastric content would retard the regulating factor of acid inhibition of the antrum and permit a continuation of secretion of acid gastric juice as a result of gastrin liberation. This is in harmony with the finding of Kesavalu and Mann,[10] who found that total intragastric drainage of duodenal contents produces a marked increase in both the volume and the acidity of the gastric secretion.

It is probable that these new findings are significant in the pathogenesis of gastrojejunal ulcer. As pointed out by one of us,[5] this lesion is clearly due to the corrosive action of the gastric content impinging on an area of jejunal mucosa in the neighborhood of the new stoma. In the absence of hypersecretion the corrosive properties of the gastric content are not sufficient to induce ulceration, as is evident by the almost complete absence of this complication when gastrojejunostomy is done in patients with carcinoma of the stomach, in patients with gastric ulcer when the gastric secretion is either normal or depressed, and in normal dogs. On the other hand, gastrojejunal ulcer is a frequent complication of gastroenterostomy for duodenal ulcer and is especially likely to occur in patients who have an abnormally large night secretion. Deviation of the alkaline duodenal content away from the region of the anastomosis, as in the Mann-Williamson procedure or when an entero-enteroanastomosis is made along with a gastroenterostomy, is now well established as a causative factor in gastrojejunal ulceration. While we are not aware of a special study on this point, it would appear very likely from the results of this investigation that a gastroenterostomy with a stoma placed in the body or fundus of the stomach would be more apt to be followed by gastrojejunal ulceration than a similar anastomosis with the stoma closer to the pylorus. We have observed several patients with gastrojejunal ulceration with a high-lying gastrojejunostomy, but we attributed these ulcers to an inadequate emptying of the stomach because of the high position of the anastomosis. The finding in this study that such a high anastomosis by itself stimulates gastric secretion suggests that this may be the more important factor. At all events, these data provide an additional reason for making the stoma in the dependent portion of the stomach, close to the pylorus, whenever a gastroenterostomy is indicated.

SUMMARY AND CONCLUSIONS

The effect of gastrojejunostomy on the secretion of gastric juice was studied in dogs provided with Pavlov and Heidenhain pouches, from which quantitative collections of gastric juice could be secured for long periods. Gastrojejunostomy was found to produce a sustained increase in gastric secretion of from 31 to 140% of the original level. This increase occurred only when the gastrojejunostomy stoma was placed in the body or fundus of the stomach and did not occur at all if the stoma was placed in the antrum close to the pylorus. The increase in gastric secre-

10. Kesavalu, A., and Mann, F. C.: Surgery **14**:578, 1943.

tion caused by a high-lying gastrojejunostomy is due to a humoral factor, since it occurred in vagus-denervated Heidenhain pouches and was entirely prevented by excision of the antrum. A high-lying gastrojejunostomy was just as effective in stimulating gastric secretion when the anastomosis was made with the posterior wall of the stomach as it was when an anterior anastomosis was made. These data suggest that a high-lying gastrojejunostomy is much more likely to be followed by gastrojejunal ulceration than is a similar anastomosis made in the dependent portion of the stomach near the pylorus.

MANAGEMENT OF CONGENITAL SCOLIOSIS

Review of One Hundred Seventy Cases

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CONGENITAL scoliosis occurs in two distinct types. In the first type the scoliosis is the result of muscular and ligamentous contractures and there is no early deformation of the axial skeleton.[1] This type of scoliosis is thought to be the result of prolonged lateral bending of the fetal spine *in utero*. It is usually corrected without great difficulty by daily stretching and by the use of a corrective plaster shell in infancy.[2] This is a rare type of congenital scoliosis. Only five patients with this type of congenital scoliosis were seen by us during the last 25 years. In each of these patients the scoliosis was corrected or greatly improved during the period of observation. None of these patients presented a serious therapeutic problem. The five cases are not included in the subsequent discussion.

In the second type of congenital scoliosis, the type commonly seen, the scoliosis is caused by congenital deformation of the spine and ribs. We have followed 165 patients, 99 girls and 66 boys, with this type of scoliosis for three years or longer. Eighty-five of these children were followed until they were fully grown, thus giving us an opportunity to study the pattern of growth in the various types of deformity. In this paper we shall discuss the various congenital deformities found in the spine and elsewhere in the body, the neurological complications, and the end-result observed in those patients followed to maturity. From these data a general plan of management has evolved.

TYPES OF VERTEBRAL DEFORMITY

Attempts at the classification of congenital spinal deformities were made by Dwight[3] and by Putti.[4] Dwight was interested primarily in anomalies of the normal segmentation of the spine. Putti, in an exhaustive study, divided congenital deformities of the spine into the following five groups: numerical variations, morphological variations, combinations of numerical and morphological variations, failures of seg-

From the Scoliosis Clinic, Children's Hospital.

1. Harrenstein, R. J.: Die Skoliose bei Säuglingen und ihre Behandlung, Ztschr. orthop. chir. **52**:1, 1929.

2. Kuhns, J. G.: Congenital Scoliosis, New England J. Med. **210**:1310, 1934.

3. Dwight, T.: Description of Human Spines, Memoirs Boston Society of Natural History, 1901, Vol. 5, pp. 237-313.

4. Putti, V.: Die angeborenen Deformitäten der Wirbelsäule, Fortschr. Geb. Röntgenstrahlen **15**:65, 1910.

mental differentiation, and gross unclassifiable changes. We have attempted to divide our cases of congenital scoliosis according to Putti's classification (Table 1). This classification, a pathological one, can be used satisfactorily only when all vertebral deformities are visible. We have found it sometimes difficult to apply in the living patient, when one must depend upon x-ray pictures which show clearly only those portions of the vertebrae which are ossified and which are not obscured by the superimposition of other bony structures.

Numerical variations, decrease or augmentation of the usual number of vertebrae, were observed as the cause of the congenital scoliosis only five times. A numerical variation alone rarely causes scoliosis. In each instance it was found in the lumbar region of the spine associated with a defect in the facets of the intervertebral spinal joints. The scoliosis was mild, the arc of the curvature never being greater than 15 degrees.

Morphological variations in the spine and ribs with the usual number of vertebrae in the cervical, thoracic, and lumbar regions of the spine were found in 50 children. Commoner was a combination of numerical and morphological changes observed in 82 patients. In this group we observed our more serious scoliosis. There changes were found most frequently in the thoracic region, but in eight patients all the verte-

TABLE 1.—*Classification of Vertebral Deformities (Putti) in 165 Patients*

Class	No.	%
1. Numerical variations	5	3.0
2. Morphological variations	50	30.3
3. Combination of numerical and morphological variations	82	49.7
4. Failure of differentiation	22	13.4
5. Gross unclassifiable change	6	3.6

brae showed deformation. In 31 children deformity was found in only one vertebra. With a combination of numerical and morphological variations, extraskeletal congenital deformities were always present.

In 22 patients there was gross failure of the segments to differentiate. The grossly misshapen vertebrae failed to show the usual characteristics of the region of the spine in which they occurred. Such abnormalities were found about the lumbosacral, the thoracolumbar, and the cervicothoracic regions of the spine. There were six patients with gross unclassifiable changes, occurring in the cervicothoracic region in two and in the lumbar region in four, with extension into the sacral area in two. In both these groups, in the failure of segmentation and unclassifiable bony masses, the spinal area was somewhat stiff. Serious curvature did not develop in these patients and their condition showed little change during the period of growth. There was, however, always considerable decrease in the expected growth in height (Fig. 1).

The manner in which vertebral deformity can take place through suppression of the proliferating mesenchyme has been shown graphically by Putti (Fig. 2). Masses of mesenchyme develop on both sides of the notochord and spread about it. These masses are later converted into the primary metameres.[5] Centers of ossification appear in these segments, corresponding in general to the divisions outlined by Putti.

5. Bardeen, C. R.: The Development of the Thoracic Vertebrae in Man, Am. J. Anat. **4**:163, 1905.

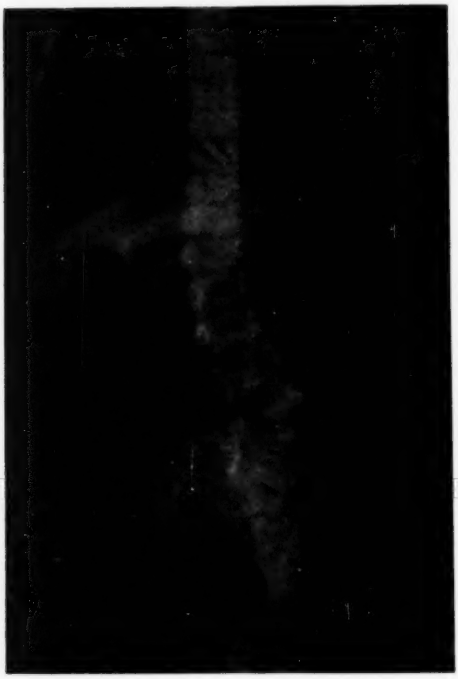

Fig. 1.—Roentgenogram of 8-year-old child. Gross unclassifiable change at lumbosacral area of spine (Putti, Class V). Curvature remained unchanged during growth, but patient was much shorter than her sisters.

Fig. 2.—Modified from Putti, showing how suppression of a preossification area can produce spinal deformities.

An alteration in rate of growth or cessation of growth in one or more of these segments leads to vertebral deformation. Costal anomalies follow faulty development of the segments which produce the transverse processes.

What causes congenital scoliosis is not known. It has been shown that various noxious substances acting upon the embryo, as well as heredity,[6] can influence the occurrence of skeletal deformities. Hormones, such as insulin, have been able to produce skeletal deformities in the chick embryo.[7] Viral diseases occurring in the first trimester of pregnancy may cause defects in the newborn child. Abnormal germ plasm,[8] changes in the amnion, intrauterine pressure,[9] circulatory disturbances in the

TABLE 2.—*Associated Congenital Deformities*

Area	No. of Patients
Head	
Special senses	4
Oral cavity	3
Gargoylism	4
Encephalocele	5
Deformity of skull	2
Upper extremity	
Elevation of scapula	10
Absence of part of limb	4
Contracture	3
Clubhand	2
Lower extremity	
Contracture	10
Clubfoot	6
Cavus	4
Dislocation of hip	4
Absence of toes	2
Thorax	
Meningocele	7
Congenital kyphosis	3
Deformity of chest	5
Absence of muscle	3
Visceral changes	
Cardiac	6
Intestinal	4
Hernia	3
Skin	
Hypertrichosis	10
Absence of breast	1
Supernumerary breast	5

placenta, and maternal nutritional disturbances[10] have been mentioned. Data are fragmentary.[11] There are no known means of preventing congenital scoliosis.

6. Hobbs, A. A.: Hereditary Factors in Multiple Congenital Deformities, Am. J. Roentgenol. **51**:677, 1944.

7. Duraiswami, P. K.: Insulin Induced Skeletal Abnormalities in Developing Chicks, Brit. M. J. **2**:384, 1950.

8. Jansen, M.: Dysostosis Cleidocranialis, J. Orthop. Surg. **3**:468, 1921.

9. Stockard, C. R.: Developmental Rate and Structural Expression: An Experimental Study of Twins, "Double Monsters" and Single Deformities, Am. J. Anat. **28**:115, 1921.

10. Warkany, J.: Congenital Malformations Induced by Maternal Nutritional Deficiency, J. Pediat. **25**:476, 1944.

11. Sawin, P. B.: Vertebral Processes and Growth Genes, Anat. Rec. **95**:183, 1946.

ASSOCIATED NONVERTEBRAL DEFORMITIES

Deformities rarely occur in the spine alone. Faulty development can usually be found in other tissues of the body. The more extensive the spinal deformations, the more frequently were congenital deformities found in other parts of the body.[12] In Table 2 we have listed the congenital deformities which were observed in other parts of the body. Many more abnormalities probably were present, but the absence of functional disturbances caused them to be overlooked. One hundred ten cases of extraspinal congenital deformities were listed. Meningocele and encephalocele were found 12 times. One patient with symptomless spondylolisthesis, Grade 1 was seen. Deformities in the limbs were common; there were six patients with clubfoot deformity, four with dislocations of the hip, and two with clubhand. Complete absence of a muscle in the spine or thorax, with no observable functional disturbance, was observed three times. Hypertrichosis of serious degree was observed 10 times, often associated with pigmentation of the skin. While all these deformities were corrected as completely as possible, only those which disturbed locomotion or balance affected the scoliosis adversely. Severe visceral disturbances or meningocele was treated in the early days of life. Most of the other conditions were treated

TABLE 3.—*Neurological Disturbances*

Type	No.
Shortening of leg	11
Spasticity in one or more limbs	7
Paralysis or weakness of muscles	7
Weakness of sphincters	6
Incontinence of urine	6
Sensory disturbance in leg	5
Trophic ulcer	2
Ataxia	2

simultaneously with the scoliosis. Hypertrichosis was controlled temporarily by shaving and was permanently removed by x-ray treatment when the child was fully grown.

NEUROLOGICAL DISTURBANCES

Neurological disturbances in 46 of these patients were studied by the neurological service (Table 3). The commonest neurological disturbance was shortening and atrophy of one leg, sometimes associated with sensory disturbances. With severe meningocele or encephalocele there was often both motor and sensory loss after operation. Other disturbances came from pressure or irritation of the cord or spinal nerves by the vertebral deformities. In four of these patients, surgical exploration was performed, and diastematomyelia[13] was found and repaired in two. Sufficient time has not elapsed to permit us to determine whether removal of pressure by operation will relieve or lessen this atrophy and shortening of the leg. In the 11 children showing such shortening, the discrepancy in length at the end of the growing period varied from $\frac{3}{4}$ in. (1.91 cm.) in the mildest to 5 in. (12.7 cm.) in the severest

12. Ehrenhaft, J. L.: Development of the Vertebral Column as Related to Certain Congenital and Pathological Changes, Surg., Gynec. & Obst. **76**:282, 1943.

13. Ingraham, F. D., and Swan, H.: Spina Bifida and Cranium Bifidum, New England J. Med. **228**:589, 1943.

case (Fig. 3). Spasticity, always of mild degree, was seen in seven children. Severe paralysis or muscular weakness was found seven times, usually after repair of serious spinal or cranial defects. No noteworthy neurological changes were observed in 14 children with the Klippel-Feil syndrome.[14] Weakness of the rectal or anal sphincter was seen six times. None of these patients required any special treatment. The condition tended to improve or to disappear as the child grew older. Only in

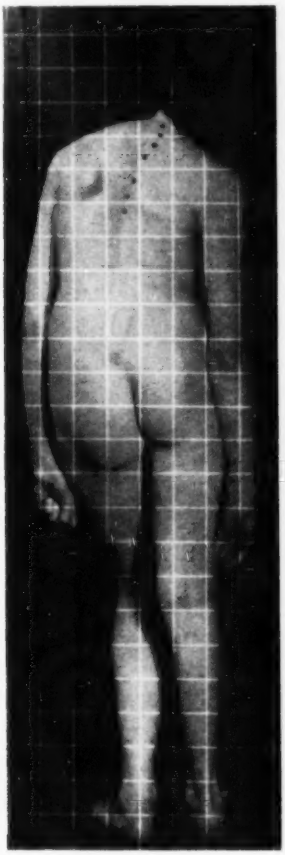

Fig. 3.—Girl, 14 years old. All vertebrae showed deformation. A thoracolumbar meningocele was repaired in infancy. Curvature remained almost unchanged but right leg was 5 in. (27 cm.) short at the completion of growth.

those children with severe muscular weakness in the thorax or abdomen or in the presence of a short leg could the neurological disturbance be considered a factor in the development of the scoliosis. The muscular weaknesses and neurological disturbances were usually treated by physical therapy. Severer neurological changes are

14. Erskine, C. A.: An Analysis of the Klippel-Feil Syndrome. Arch. Path. **41**:269, 1946.

found in many extensive meningoceles, but patients with such a condition do not attend an ambulatory scoliosis clinic.

PROGRESSION OF THE SCOLIOSIS

The lateral curvature in these children was usually of small degree at first, and in only three was there significant lateral displacement of the thorax originally. The subsequent development of the deformed vertebra to greater or less distortion determined the progression of the scoliosis. Nonaxial deformities (ribs or limbs)

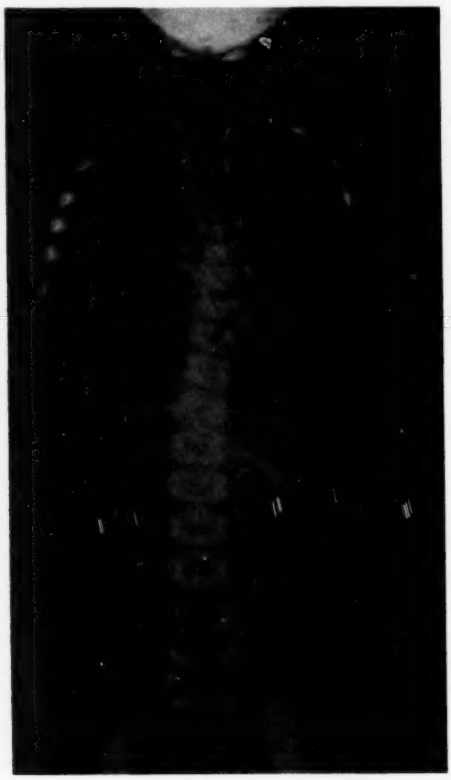

Fig. 4.—Congenital scoliosis in a child 10 years old. Fourth to eighth ribs are absent on right side. This curvature showed no appreciable change during eight years of observation.

play a minor role. Costal deformities found in all cases of extensive congenital scoliosis never disturbed thoracic mechanics seriously.[15] We have observed the same convexity of curve and similar progression with fused ribs, absence of ribs, or supernumerary ribs[16] (Fig. 4). Examination in the presence of severe thoracic

15. Sternberg, H.: Zur Prognose angeborener Skoliosen, Arch. orthop. u. Unfall-Chir. **33**:307, 1933.

16. Bisgard, J. D.: Deformities of Chest and Spine Resulting from Thoracic Disease and Operation, Am. J. Surg. **54**:317, 1941.

deformity failed to show any noteworthy muscular weakness. The absence of a muscle in three patients did not seem to lead to more serious curvature, the adjacent muscles taking over the function of the absent muscle. Scoliosis resulting from congenital deformities of the vertebrae is governed by the same mechanical principles as in other types of scoliosis.[17]

Most of our patients had a single lateral curvature originally, oftenest in the thoracic region. With growth and with increase in the original curve, compensatory curves developed (Fig. 5). In 67 patients, multiple curves caused by scattered deformities were present at birth. As a rule, the children with many widely separated deformities in the spine and multiple curves showed a slower increase in the progression of the curvature. The severest curvature was seen with deformities on one side of the spine, chiefly in the thoracic region. Deformities in the lumbar spine were serious only when they were associated with displacement of the entire

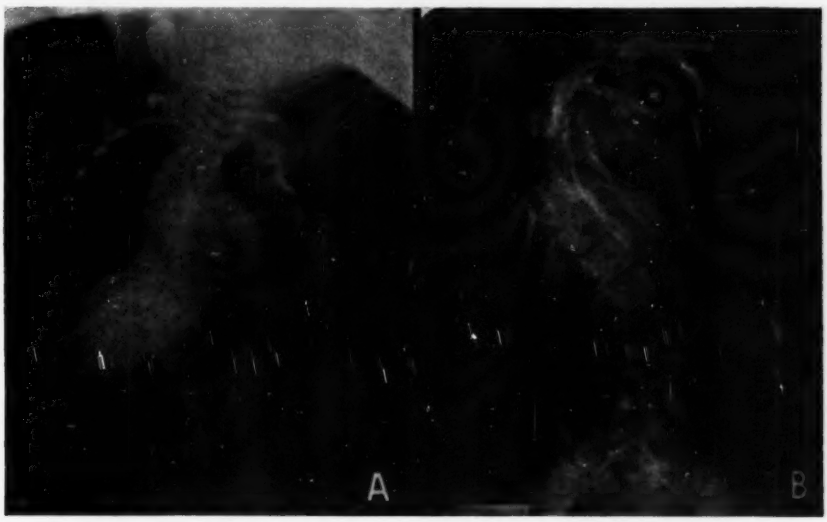

Fig. 5.—*A*, congenital scoliosis in child 4 years old. Deformation of all vertebrae. Fusion and absence of ribs on left side. *B*, same patient at 16 years of age. Spine is somewhat stiff. Thorax is balanced well over pelvis. This patient, now aged 26, is a social worker.

thorax. Cervical deformities alone never led to severe scoliosis (Fig. 6). Klippel-Feil syndrome, a decrease in the number of cervical vertebrae, remained unchanged throughout the period of growth. The only noteworthy change was a broadening of the base of the neck. Vertebral anomalies on opposite sides of the spine tended to compensate for each other. In six patients followed throughout the growing years, a practically straight spine developed.

TREATMENT

The management of patients with congenital scoliosis depends upon the degree of curvature found originally, upon the degree and location of the vertebral deformi-

17. Steindler, A.: Mechanics of Normal and Pathological Locomotion in Man, Springfield, Ill., Charles C Thomas, Publisher, 1935.

ties, and upon the associated abnormalities. Certain patterns of progression were observed with mild individual variations. The patients could be divided into the following categories: (1) those who required observation only; (2) those who

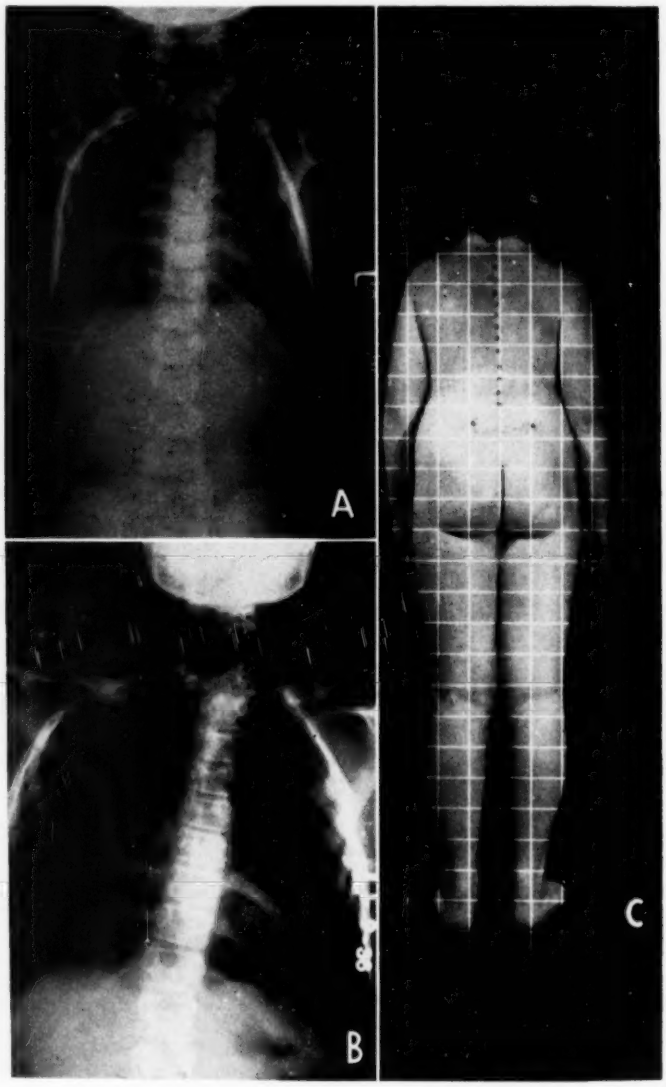

Fig. 6.—*A*, deformities of vertebrae in cervical and cervicodorsal regions of spine in a child 8 years old. *B*, roentgenogram of same child at 16 years of age. *C*, photograph of child 16 years old, showing an almost straight spine, but with widening at the base of the neck.

required physical therapy and at times support to the spine, and (3) those who required surgical correction of their spinal deformity.

All patients were examined at least twice a year through the growing period, with measurements being tabulated and pictures and x-rays made.[18] Congenital scoliosis which required observation alone was that associated with deformities in the cervical spine, chiefly the Klippel-Feil syndrome. No treatment was needed for numerical variations in the lumbar spine and in the presence of large unclassifiable lesions (Putti, Class V). The congenital scolioses which required physical therapy and, occasionally, support to prevent or to lessen an increase in the curvature were mostly of the morphological type, and combinations of morphological and numerical variations. Most of these vertebral deformities were located in the thoracic region and were multiple, often widely distributed deformities. The most rapid progression of the curvature was seen with single deformities in the upper or mid-thoracic region of the spine. The patients who required surgical correction of their curvatures and spinal fusion were patients who had been given physical therapy and support but had shown progression of their curvature in spite of this. Many of these patients showed originally a single large thoracic curve with lateral displacement of the thorax greater than ½ in. (1.3 cm.) from the midline or severe double curves which did not become balanced over the pelvis.

The scoliosis seen with congenital vertebral deformity changes slowly. The spine is stiff, particularly about the vertebral deformity. Any progression of the curve or improvement of it does not occur rapidly. There is always ample time for careful study of the deformity and the planning of a program of treatment. At least two-thirds of the patients will show no great change in the spinal curvature whether treatment is given or not. No matter how mild the curvature, the patient should be seen at least every six months, and accurate records of the curvature should be kept. If there are no symptoms, if the general posture is good, and if there is no measureable progression in the scoliosis, no treatment is necessary. However, the patient should be kept under observation until full growth is obtained. The critical periods are those of rapid spurts of growth, particularly during adolescence.[19] At such times increase in the curvature is likeliest to occur. Usually the associated deformities and neurological disturbances will have been corrected or improved before this time. Their correction is essential for the health of the child and for accurate evaluation of the scoliosis.

If the general alignment of the body or the curvature grows worse, treatment is indicated. The indication for treatment is, primarily, a measurable increase in the curvature of the scoliosis and, secondarily, an impairment in the alignment of the body.[20] General postural exercises have been found most effective for correction of the posture and for improvement in the general alignment of the body. These postural exercises are combined with mobilizing exercises to prevent, rather than to correct, any contractures in the spinal musculature. Exercises do not lead to decrease in the curvature, but they do lead to increased strength and coordination in the supporting musculature.[21] In most instances a certain degree of equalization (compensation) of the curves occurs. The curves tend to become similar in degree and tend to balance the head and torso more effectively over the pelvis. With better

18. Cobb, J. R.: Treatment of Scoliosis, Connecticut M. J. **7**:467, 1943.

19. Kuhns, J. G.: Physiological Scoliosis, Arch. Pediat. **55**:343, 1938.

20. Blok, G.: Over aangeboren misformingen van de wervellichamen, Nederl. tijdschr. v. geneesk. **91**:1622, 1947.

21. Arvin, A. M.: Prophylaxis in Scoliosis, J. Bone & Joint Surg. **34**:47, 1952.

balance of the thoracic displacement, improvement in bodily alignment and balance was observed. In a small number of children with lateral tilt of the pelvis or shortness of one leg, a lift on the shoe of the short leg was needed to correct the balance of the spine over the pelvis.[22]

Shift of the center of gravity and lateral displacement of the thorax can be changed temporarily by apparatus. Such apparatus to be effective must be worn constantly for a number of months. Plain plaster jackets or corsets were wholly ineffective in improving the curvature or shifting the trunk. The only value of such simple apparatus was to relieve muscular fatigue in the spinal area. The most effective apparatus was a turnbuckle jacket or brace which[23] temporarily shifted the thorax laterally. In most instances the wearing of this type of support for several years lessened the measurable progression of the spinal curvature. In 10 patients the

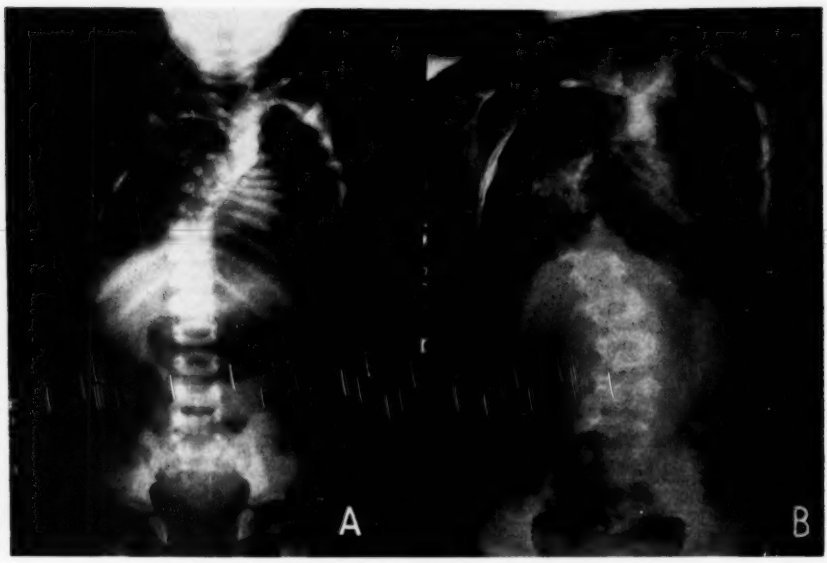

Fig. 7.—*A*, congenital scoliosis in 4-year-old child, with mild double curvature in upper thoracic region. *B*, same child 10 years later. Both curves have increased greatly, and a compensatory lumbar curve is present. With increasing deformity and displacement of thorax, forceful correction and spinal fusion are indicated.

shift in weight was followed by a more nearly symmetrical growth in the deformed vertebrae. Once the wearing of apparatus was begun, it was continued until full growth was attained, or until it was proved inadequate and the child was recommended for surgical treatment. In 94 children in whom turnbuckle jackets or braces were used, no increase in the curvature was observed after the use of a jacket in 26. In 53 there was an increase in the curvature of less than 20 degrees. In 26 patients the curvature increased greatly in spite of the apparatus, with marked

22. Kleinberg, S.: Treatment of Structural Scoliosis, Bull. Hosp. Joint Dis. **9**:158, 1948.

23. Barr, J. S., and Buschenfeldt, K.: Turnbuckle Brace, 3 Point Pressure Brace for Corrective Treatment of Ambulatory Cases of Scoliosis, J. Bone & Joint Surg. **18**:760, 1936.

lateral displacement of the thorax. Twenty of these patients came later to forceful partial correction of their deformity and spinal fusion. Six children had no symptoms and fairly symmetrical curves at maturity, and no further treatment was required.

The indications for forceful correction and spinal fusion are the same in congenital scoliosis as in other forms of scoliosis. The general plan is to advise operation in adolescent children when the curvature is greater than 30 degrees and there are not equalizing compensatory curves, when deformity is increasing, and when there is an inch or more of lateral displacement of the thorax from the midline. Fusion was rarely performed in small children. Three of our patients were operated on at an early age in other clinics and came to this clinic later for further treatment of increasing deformity. Before operation the curvature is corrected as far as possible by turnbuckle jackets, and then spinal fusion is performed. In most instances the curvature is corrected less than half of the usual amount. The stiff spine and the spinal deformities usually do not permit a great amount of correction. Apparatus is worn postoperatively until we are certain that the spinal fusion is solid and that no further deformity will occur. Exercises are then given to strengthen spinal musculature and to improve the alignment of the body as much as possible (Fig. 7).

TABLE 4.—*Children Observed Throughout Growth*

Area Deformed	Change in Curvature		
	Less Than 5°	Less Than 30°	Greater Than 30°
Cervical region	4	4	0
Upper thoracic region	0	12	12
Lower thoracic region	3	12	14
Lumbar region	6	10	5
All vertebrae involved	0	2	1

OBSERVATION TO MATURITY

Eighty-five of these patients were under observation until full growth had been attained. The most descriptive way of classifying these children is by the location of their curve or by the area in which the greater amount of spinal deformation was present (Table 4). Most of the children showed no great change in the scoliosis. Deformities and curvature in the cervical or cervicodorsal region of the spine never required much treatment. They led to a little shortening of stature and usually a broadening at the base of the neck, but no observable disturbance in function. Deformities in the upper or mid-thoracic region of the spine led to the greatest number of serious deformities. Almost half these patients showed serious lateral displacement of the thorax. This tended to increase and made difficult balance of the spine over the pelvis or development of equalizing compensatory curves. All types of apparatus were ineffective in preventing increase in the curvature, although supports which tended to lessen the lateral shift of the thorax slowed the progression of the curvature. Deformities in the lower thoracic or thoracolumbar spine were controlled somewhat more easily. Compensatory curves above or below the original deformity tended to balance the deformed area and lessened thoracic displacement. Deformities in the lumbar region led to serious deformity in only five of the patients followed to maturity. Here, there was lateral displacement of the thorax with no

equalizing compensatory curve on the other side of the spine. In most of them compensatory curves quickly developed above the deformity, and most of the spines remained well balanced over the pelvis.[24]

COMMENT

No rigid plan for the management of congenital scoliosis can be laid down. We have no previous studies for comparison. No large number has been reported previously, nor have many patients with congenital scoliosis been followed to maturity. There are usually a number of other factors which must be taken into account besides the lateral curvature. Chief among these are deformities elsewhere in the body, weakness and paralysis in the supporting muscles, shortness of one leg, and, occasionally, trophic disturbances. Our experience confirms previous reports that most of the disturbances, as well as the congenital scoliosis, follow a benign course. The disabilities change slowly. While long observation has demonstrated that numerical variations, cervical deformities, failures in differentiation, and gross unclassifiable deformities (Putti, Class I, IV, and V) rarely show much if any progression of the curve, patients with this deformity need to be kept under observation during the growing period.[25] Most treatment will be required by those with morphological variations and combinations of morphological and numerical variations (Putti, Class II and III). About one-half of the latter groups will show increase in the curvature and the lateral displacement of the thorax. A small number of these should have as much correction of their curvature as possible, followed by fusion of the spine.[26] While there will be a slight increase in deformity in a few of these children due to growth of the deformed vertebrae, this increase is never great. In the past, attempts have been made to remove the deformed vertebra when one or a few deformed segments were present in one area.[27] This has not resulted in improvement in the majority of instances and is no longer attempted. More recently stapling across deformed vertebrae has been reported, with some improvement in the growth of the vertebral deformity.[28] Longer observation is necessary before the effectiveness of this procedure can be evaluated.

SUMMARY

Congenital scoliosis occurs in two types: a rare type, caused by muscular and ligamentous contractures, and the common type, caused by congenital deformities of the vertebrae. Congenital deformities of the spine are frequently associated with other deformities and with neurological disturbances, which make the management

24. Steindler, A., and Ruhlin, C. W.: The Conservative Compensation Derotation Treatment of Scoliosis, J. Bone & Joint Surg. **23**:67, 1941.

25. Smith, E. M., and Shields, C. D.: Conservative Treatment of Scoliosis in Selected Cases, Arch. Phys. Med. **29**:709, 1948.

26. Risser, J. C.: Important Practical Factors in the Treatment of Scoliosis, in American Academy of Orthopaedic Surgeons Lectures on Reconstructional Surgery, Ann Arbor, Mich. Edwards Brothers, Inc., 1948, Vol. 5, pp. 236-248.

27. Edwards, P., and Von Lackum, W. H.: Surgical Treatment of Scoliosis in American Academy of Orthopaedic Surgeons Lectures on Reconstructional Surgery, Ann Arbor, Mich., Edwards Brothers, Inc., 1948, Vol. 5, pp. 236-248.

28. Nachlas, I. W.: The Cure of Experimental Scoliosis by Directed Growth Control, J. Bone & Joint Surg. **33A**:24, 1951.

of the scoliosis more complicated. Most patients with congenital scoliosis will show little change in their curvature and require only periodic observation to determine that the curvature has not increased. In most of those who show increase in curvature and lateral displacement of the thorax, serious deformity can be lessened by physical therapy and proper support. A small number with serious deformity can be improved by forceful partial correction of their curvature, followed by spinal fusion.

RECURRENCE IN CARCINOMA OF THE COLON AND PROXIMAL RECTUM FOLLOWING RESECTION FOR CARCINOMA

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ALL SURGEONS are aware of the relatively high incidence of local recurrence at the suture line in primary resection and end-to-end anastomosis for carcinoma of the colon and proximal rectum. I am of the opinion that at least half of the recurrences at the suture line are local implants and I have previously called attention to this possibility.[1] It is obvious that there is enough manipulation of the tumor during the resection to result in desquamation of numerous cancer cells from the primary lesion. Moreover, we now know with the aid of the Papanicolaou stain that cancer cells desquamate profusely from ulcerating tumors. Although it is unlikely that these desquamated cells would become implanted on normal mucosa, it may be assumed that they might become implanted on open wounds or ulcerated areas and grow. There is ample evidence that cancer cells can be implanted in breast wounds during radical mastectomy, and in wounds following many other types of radical operation for cancer. If implantation can occur in certain types of operation, it is logical to assume it might take place in others. An opportunity for implantation might develop in any operation in which the bowel was cut across. It may be assumed that the number of desquamated cells would be greater in the portion of the colon distal to the tumor because the fecal stream would carry them distally. However, as illustrated in Figure 1, it is conceivable that cells might be forced upward into the part of the colon proximal to the lesion if the tumor is located in an area which allows drifting of cells proximally by gravity as they are broken off by manipulation during the operation.

My colleagues and I have gone over records at Illinois Research Hospital and find that in 55 consecutive patients having local resection for carcinoma of the colon and proximal portion of the rectum over a five-year period between 1944 and 1950 (exclusive of Miles operations) there was an incidence of local recurrence equal to 16%. In this group of nine recurrences, six occurred at the suture line, constituting an incidence of 10.9% in which recurrence by implantation was possible. In the other three patients the recurrence was distal to the suture line and/or associated with generalized metastases. Dukes and associates [2] have recently studied the recurrences

Jerome Lipin assisted in reviewing records of patients.

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1. Cole, W. H.: Measures to Combat the Menace of Cancer, Am. Surgeon **17**:660 (July) 1951.

2. Goligher, J. C.; Dukes, C. E., and Bussey, H. J. R.: Local Recurrences after Sphincter-Saving Excision for Carcinoma of the Rectum and Rectosigmoid, Brit. J. Surg. **39**:199 (Nov.) 1951.

in their patients having local resection and concluded that about half probably developed from implants. In 162 patients having local resection of the proximal rectum followed by end-to-end anastomosis or colostomy and inversion of the rectal stump (Hartmann operation) local recurrence had already been found in 16, or 10%, and another resection was carried out in 9 of the 16. These authors studied an additional 7 cases (total 23) of local recurrence obtained from other hospitals. In two of their cases carcinoma became implanted in the soft tissues of the abdominal wall or perineum.

EVIDENCE IN FAVOR OF IMPLANTATION AS CAUSE OF RECURRENCE AT SUTURE LINE

If a recurrent growth were metastatic in origin, particularly from a lymph node, it is obvious that the tumor would show up first on the outside wall of the colon and thus compress the colon or ulcerate into it from the outside. We have observed lesions of this type, but they are much less common than the recurrences developing

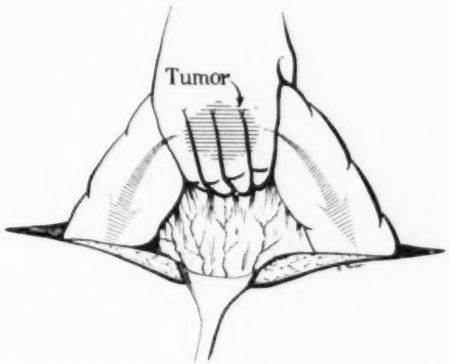

Fig. 1.—Manipulation during resection of a tumor of the colon at times is severe, thus giving rise to desquamation of cells from the tumor in either direction.

in the mucosa at the suture line. Dukes and associates, who likewise have been impressed with the possibility of recurrence by implantation, found the tumor growing in from the outside in only 4 of the 16 local recurrences, or 25%.

It is well known that in the colon growth of the cancer seldom travels a significant distance in the wall as it does in the stomach. For this reason one should not expect a very high incidence of recurrence due to inadequate excision since the surgeon usually removes at least 2 in. (5 cm.) of normal bowel on both sides of the colon. Moreover lymphatic spread almost never extends a significant distance distal to the lesion. Dukes and associates [2] found a lymphatic spread more than ¾ in. (2 cm.) distal to the lesion in only 2% of their cases. Gilchrist and David [3] found that lymphatic spread was noted 1 to 5 cm. distal to the tumor in only 4.6% of their cases. In view of this tendency for the cancer to grow proximally instead of distally,

3. Gilchrist, R. K., and David, V. C.: A Consideration of Pathological Factors Influencing Five Year Survival in Radical Resection of the Large Bowel and Rectum for Carcinoma, Ann. Surg. **126**:421 (Oct.) 1947.

one would expect very few recurrences to arise from the distal loop because of inadequate excision. Yet Dukes and associates noted four recurrences in the turned-in stump of the rectum in 31 patients on whom the Hartmann operation was performed. This suggests that implantation may be a more significant factor than incomplete excision.

If local recurrence has its source in inadequate excision but does not arise from the distal segment, then it must develop in the proximal segment. However, we have quite good evidence that this does not occur very frequently. I have never seen a recurrence in a colostomy following excision of carcinoma of the rectum except in two patients who had polyps in the colon including the site of the colostomy. Dukes and associates report encountering only three recurrences at the colostomy site in over 2,000 colostomies performed in association with excision of the rectum for carcinoma. When resections are performed for lesions located at or slightly above the peritoneal reflection, the surgeon often does not decide whether to do a resection and end-to-end anastomosis or a Miles operation until the lesion and adjacent tissue

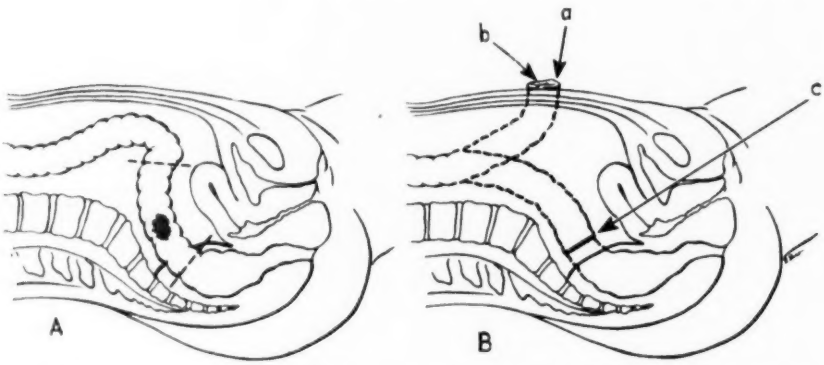

Fig. 2.—*A*, in lesions just above the peritoneal reflection, either a Miles operation or resection with primary anastomosis may be performed. *B*, when a Miles operation is performed (*a*), recurrence rarely if ever develops at the colostomy site (*b*), whereas it does so in 5 to 15% of cases of resection with primary anastomosis (*c*). If recurrence were caused primarily by inadequate excision, it should develop frequently in the colostomy, particularly since the tumor metastasizes proximally.

have been removed. Usually the proximal segment has been or will be severed at the same point regardless of which procedure will be performed (Fig. 2).

It appears very significant that when this proximal loop of sigmoid is brought out as a colostomy cancer does not develop in it, but if this proximal segment is brought down to meet the distal segment in an end-to-end anastomosis, local recurrence may develop in 5 to 15% of cases (Fig. 2). If one accepts implantation as the explanation for recurrences in the primary anastomosis, one must assume that something about the procedure of a colostomy eliminates the possibility of recurrence. In my opinion, there are two reasons why cancer might not develop at the colostomy site by means of implantation. The first is related to the fact that this area is proximal to the lesion and is not exposed to so many desquamated cells. The second reason is that the bowel is crushed with a clamp and brought out as a colostomy without any sutures being taken through the wall. Even though some live cancer

cells might be present at the area crushed by the clamp, it is probable that in this necrotic tissue resulting from the crush of the clamp the cancer cells could not grow. On the other hand, when an end-to-end anastomosis is performed, all the bowel is sectioned cleanly, and in addition sutures pass in and out through the wall from inside to outside throughout the process of completing the first row of sutures. It seems likely that the puncture site in the wall of the colon might be a better medium for growth of the cells than the cut edge of the colostomy, particularly since in the latter case they would be imbedded in necrotic tissue.

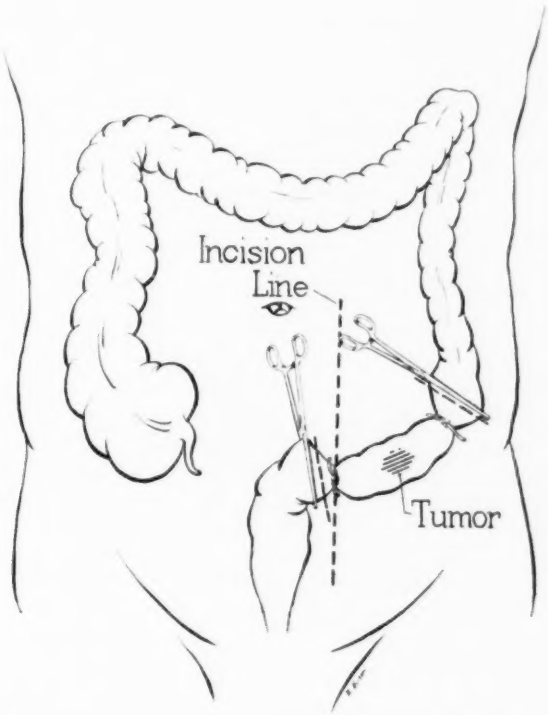

Fig. 3.—The first step in an effort to prevent recurrence from implantation is to tie a tape ligature around the bowel several centimeters above and below the tumor.

Although very few data are available relative to the comparison of the local recurrence rate in patients having resection by the radical Mikulicz operation and those having resection with primary end-to-end anastomosis, most surgeons are of the impression that recurrence is uncommon after the Mikulicz operation. Only one of our local recurrences followed a radical Mikulicz resection; it was found as a tiny nodule at the time of colostomy closure three months after the resection. If local recurrence were due to inadequate removal of bowel wall, then local recurrences should be very common following the Mikulicz operation because the removal of bowel wall is usually sharply limited by this operation. One might ask why the tumor cells do not become implanted frequently at either end of the bowel in a

Mikulicz operation if the implantation theory is significant. The answer to this would lie in the explanation previously given in that a large crushing clamp is placed across the bowel proximal and distal to the lesion, and any cells trapped between the blades of this crushing clamp would, of necessity, be imbedded in necrotic tissue resulting from the crush. This necrotic tissue would obviously be a very poor medium for the growth of a cell by implantation.

Consideration of the above data convinces me that if implantation of cells takes place, it must do so on fresh tissue, and the best media would probably be in the puncture holes made in the bowel wall during the completion of the first row of sutures, because the cells could then be dragged in with the sutures and become imbedded inside the healthy vascular bowel wall.

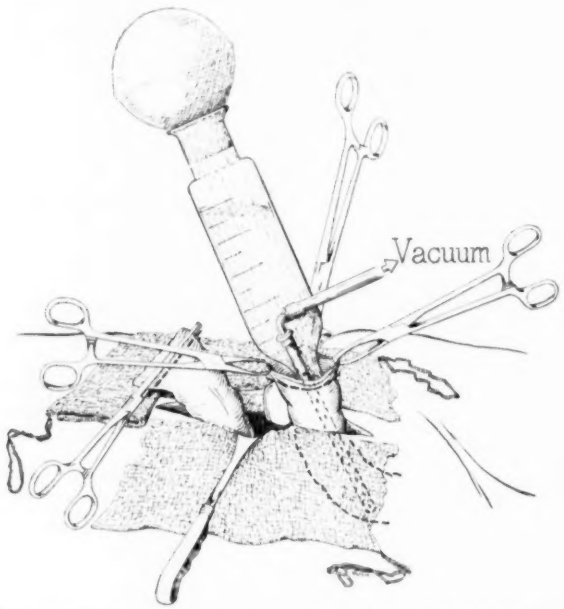

Fig. 4.—After the bowel and mesentery are resected each end of the bowel is irrigated thoroughly for three to five minutes with distilled water. After this irigation, a small segment is cut off each end to minimize the possibility of implanting cells into this cut surface of the bowel.

METHODS OF PREVENTING IMPLANTATION OF CANCER CELLS AT SUTURE LINE

If implantation of cancer cells takes place at the suture line, prevention should obviously be directed toward elimination of the cells in the lumen of the bowel at the site of section of the bowel and application of sutures. This can be achieved by any of several different methods, none of which may be entirely satisfactory.

I have recently adopted the procedure of applying a tape ligature around the bowel several centimeters proximal and distal to the tumor before any manipulation is carried out (Fig. 3). The bowel and mesentery are then mobilized for resection. A clamp is placed on the proximal and on the distal segment of bowel beyond the

ligature as shown in Figure 3. This procedure should eliminate the possibility of loose cancer cells proximal to the tumor except those carried proximally by a preoperative enema. It is probable that cells lying free in the lumen would not live longer than a few hours, but if an enema is given on the morning of the operation as is a common custom, there might be live cancer cells anywhere in the proximal colon at the time of operation. After the tumor and adjacent tissue have been resected, the bowel is opened by removing the clamp and applying Allis forceps to the edge. The lumen of the bowel is then irrigated with distilled water for three to five minutes, and the fluid is aspirated during the irrigation as shown in Figure 4. A small segment of the end of the bowel is then excised to eliminate the possibility of cancer cells being trapped and implanted at the point where the crushing clamp had been applied. This procedure is carried out on the proximal segment of bowel as well as the distal segment.

We have not used any chemicals in our attempt to destroy loose cancer cells, but if we did, we should probably choose a weak solution of iodine tincture. However, irrigation with 0.2% mercury bichloride has been recommended by Dukes and associates. They put a clamp on the distal segment of bowel and irrigate for five minutes with mercury bichloride by insertion of a catheter through the anus. At the completion of the irrigation they cut across the bowel distal to the clamp, thus having a field reasonably free from loose cancer cells at the point where the section is made and sutures are taken. Although it is not probable that sufficient mercury bichloride would be absorbed from the rectum during the irrigation to be detrimental, yet it must be remembered that mercury is an active cellular poison.

SUMMARY

I have been impressed with the high incidence of local recurrence at the site of anastomosis when resections of the colon are carried out. It appears that in a great many cases this local recurrence may be due to implantation of live cancer cells either displaced by manipulation during the operation, or desquamated from the tumor into the lumen before the operation. Dukes and associates have reported a local recurrence of 10% in 162 patients, although they thought no more than half the recurrences could be caused by implantation. In our series of 55 patients with resection of the colon studied during the past several years, the incidence of recurrences at the suture line was 16 per cent, although local implantation would have been possible in only 10%.

One of the arguments which might be presented to support the theory of implantation is the fact that local recurrence practically never is found at the end of a colostomy performed during resection of a cancer of the rectum and lower sigmoid. If inadequate excision of bowel wall was the explanation of recurrence at the line of resection, we should certainly see instances of recurrence in the colostomy. I have never seen any recurrences after colostomy for excision of carcinoma of the rectum except in one or two cases in which numerous ulcerated polyps were present. This point becomes more significant when it is realized that the extent of resection of the tumor is usually not altered by the question as to whether the proximal loop is brought out as a colostomy or is brought down to the distal loop for an end-to-end anastomosis. As a matter of fact, a wide resection proximal to the tumor often leaves such a short segment of mobilized colon (especially in the descending colon of fat patients) that colostomy is not very practical and resection with end-to-end anastomosis is preferred. In this case, recurrence should be more frequent in colostomies

than when end-to-end anastomosis is performed, if local recurrence were caused by inadequate excision of bowel and mesentery. However, as already indicated, such is not the case.

I have adopted the procedure of applying a tape ligature several centimeters proximal and distal to the tumor before any manipulation incident to the operation is carried out. As the diseased bowel is being resected, clamps are applied to the colon proximally and distally, and each segment is irrigated thoroughly with distilled water before anastomosis is performed. After the irrigation, a small segment is resected from either end to eliminate the possibility that cells may have been trapped in the wall at the site of application of the clamp. However, as stated above, it is probable that cells trapped in this necrotic tissue will not grow. Nevertheless it would appear advisable to cut off an additional short segment since it can be done in a few seconds and would permit section of the bowel and application of sutures in a clean field relatively free from loose cancer cells.

PATHOGENESIS OF VALVULAR ENDOCARDITIS

I. Production of Acute Cardiac Valvular Lesions by a Large Arteriovenous Shunt

II. Effects of an Arteriovenous Shunt on Removal of Bacteria from the Blood Stream

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G. P. KERBY, M.D.
AND
W. C. SEALY, M.D.
DURHAM, N. C.

THE FACTORS underlying the pathogenesis of valvular endocarditis may be divided into two large groups, those related to valvular disease and those related to the entrance of bacteria into the valvular lesion. In studying this problem, Nedzel [1] reported that valvular lesions occurred in dogs from the repeated use of vasopressin injection (pitressin®). Trauma, due to an increased cardiac work load during the pressor episodes, was advanced as the important initiating factor in that it caused endocardial damage which then served as a nidus for the development of infection. Lillehei, Bobb, and Visscher [2] reported endocardial lesions and bacterial infection of those lesions in animals with arteriovenous fistula.

The present study was undertaken to further understand the nature of these valvular lesions and to determine the effect of the altered circulation incident to these large arteriovenous fistulae on the ability of the animal to remove bacteria from the blood stream. Two sets of experiments were carried out, one confirming the development of the endocardial lesions and showing that they occur early after the fistula is opened, with another showing that large fistulae had no effect on the extent of removal of bacteria in the splanchnic area but did alter the time required to remove them from the blood stream.

METHODS

Healthy mongrel dogs weighing 8 to 15 kg. were used. All dogs were estimated to be less than 5 years of age. Pentobarbital sodium intravenously was used as an anesthetic agent, and all operative procedures were carried out under aseptic technique. The anastomoses were performed with a continuous suture of 5-0 silk. The openings were constructed between the aorta and the vena cava inferior to the renal vessels. In five animals the fistula measured 2 to 4.5 cm. in length. Two of the animals were killed within six hours. The remainder died within 12 to 18 hours. Autopsies were performed on all dogs immediately after death. In two animals, India ink was injected prior to death.

Aided in part by a grant from the American Heart Association and the Anna H. Hanes Fund.

From the Division of Thoracic Surgery and the Department of Medicine, Duke University School of Medicine.

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2. Lillehei, C. W.; Bobb, J. R. R., and Visscher, M. B.: The Occurrence of Endocarditis with Valvular Deformities in Dogs with Arteriovenous Fistulas, Ann. Surg. **132**:577-590, 1950.

A second group of three animals was studied, two with a large arteriovenous fistula between the aorta and the inferior vena cava measuring 2.5 and 4 cm. in length and one with a very small fistula measuring 5 mm. in diameter. These fistulae were constructed so that they could be opened and closed at will. In these animals an infusion of a Micrococcus aureus, coagulase-positive, was started and maintained until a constant arterial level was obtained. When this level was reached, the bacterial infusion was stopped, and the rate of fall of the arterial bacterial level was measured. This was repeated twice, with the fistula opened and closed.

The third group of animals was prepared by production of chronic bilateral iliac fistulae measuring 2 to 2.5 cm. in length. After two to three weeks a constant bacteremia was instituted in these animals by the infusion of bacteria from a motor-driven syringe. Radiopaque catheters were passed by fluoroscopic visualization into the hepatic veins from an incision in the jugular vein. The extent of bacterial removal in the splanchnic area was determined by comparing the hepatic and the arterial blood levels, as described in a previous publication.[3]

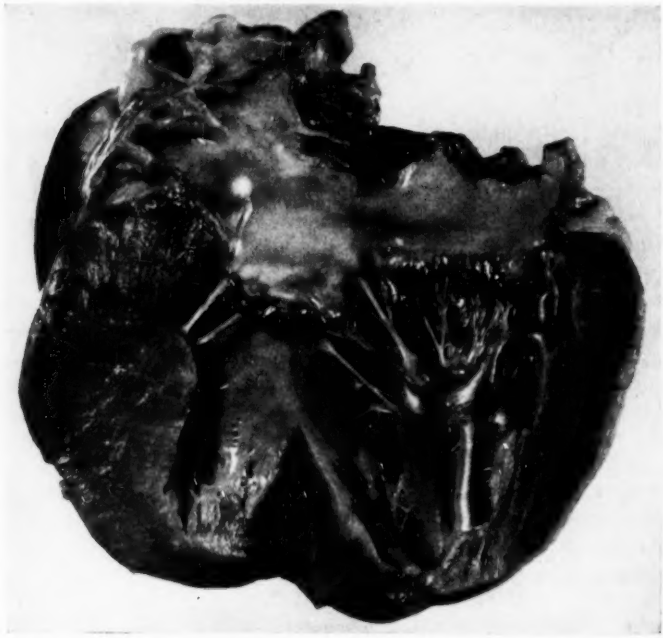

Fig. 1.—Interior of left ventricle, showing hemorrhagic edematous beading along edge of cusps of mitral valve. Some edema of chordae tendineae is present. These changes occurred six hours after construction of a large arteriovenous fistula.

RESULTS

In all animals examined at the end of the experiments, the right ventricle was markedly dilated, and the left ventricle was slightly dilated. Endocardial lesions were found in all animals in the first group. Figures 1 and 2 illustrate the type of lesions noted, and such lesions were present in both the mitral and the tricuspid

3. Martin, S. P.; Kerby, G. P., and Holland, B. C.: A Method for Measuring Removal of Bacteria from the Blood by the Various Organs of the Intact Animal, Proc. Soc. Exper. Biol. & Med. **72**:63-68, 1949.

valves. These lesions ranged from minute flat endocardial hemorrhages to cherry-red nodules 3 to 4 mm. in diameter along the free margin of the mitral and the tricuspid valves. Occasionally, similar lesions were noted in the endocardium of the left ventricle. Microscopic sections of the valves showed edema and subendocardial hemorrhages. No cellular infiltrate was present, and infiltration was not expected, since the lesions were only a few hours old. In the two animals receiving India ink, carbon particles were found intracellularly and extracellularly on the surface of the lesions and in the hemorrhagic valvular lesions.

In the bacterial clearance studies, results of the rapidity of clearing of the blood stream in one trial for each animal are reported in the accompanying Table. Similar

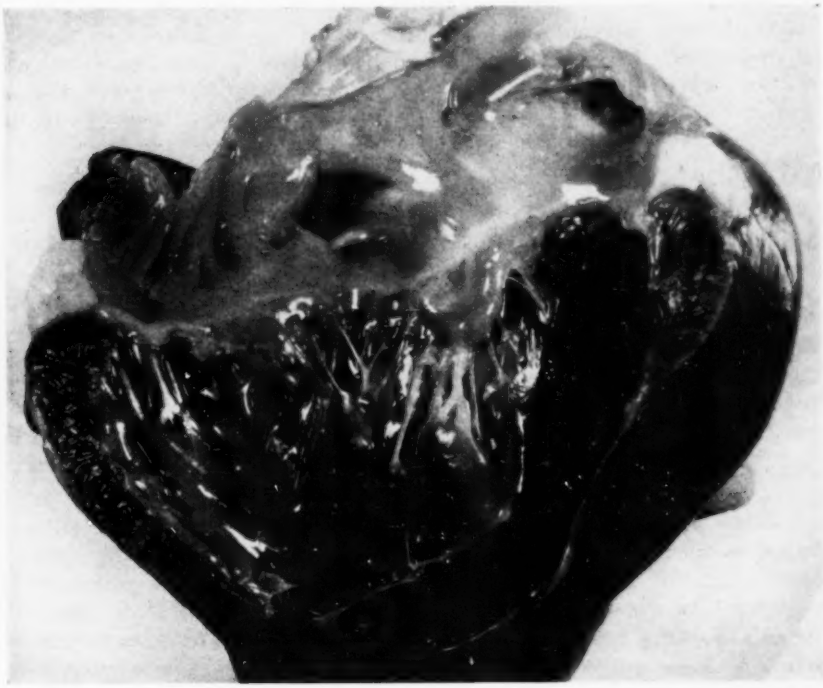

Fig. 2.—Interior of right ventricle. Edges of valve cusps are edematous and show a ridge along edge. Chordae tendineae are markedly thickened. Those changes occurred approximately 12 hours after construction of a large arteriovenous fistula.

results were obtained on other trials. Cultures are recorded at 3, 6, 10, and 15 minutes after cessation of bacterial infusion. The number of organisms recorded at 0 time in each case was considered to be 100%, and the number recorded at each time interval thereafter is recorded as the percent of the original level. There was a consistent and significant difference in the rapidity of clearing the blood stream with the large fistula open and closed. In the animal with the small fistula, there was no difference. In the third group of animals, it was noted that the extent of removal in the splanchnic system is 93 and 84% as compared with a control level of 74 ± 16%. There is no statistical difference between this and a group of normal animals.

COMMENT

In the pathogenesis of bacterial endocarditis, injury to the heart valves has long been considered to be of primary importance.[4] In experimental animals, bacterial endocarditis has been produced in this way. Valvular injury and bacterial vegetations have also been produced without direct injury to the valves by the repeated injection of bacteria [5] and by repeated pressor episodes induced by vasopressin injection.[1] Rosenow found endocardial lesions of the valve leaflets after the repeated injections of virulent or heat-killed cocci into rabbits. Occasionally, bacterial vegetations were found. He felt that these lesions were embolic. Wadsworth [6] was able to produce endocardial lesions in immunized horses by the injection of heat-killed pneumococci. Dick and Schwartz,[7] and Blahd, Frank, and Saphir [8] were able to produce bacterial endocarditis in a high percentage of dogs by the repeated injection of virulent bacteria. Although the mechanisms involved in these experiments are not clear, it is possible to speculate that endothelial damage occurred either through sensitization of the valvular endocardium or through trauma resulting directly from the increased cardiac work load during the febrile response following the injection of the material.

TABLE 1.—*Bacterial Clearance Studies in Dogs with an Arteriovenous Fistula*

Dog	1 Large Fistula				2 Large Fistula				3 Small Fistula			
Fistula	Closed		Open		Closed		Open		Closed		Open	
Time in Min.	No. of Bacteria	%	No. of Bacteria	%	No. of Bacteria	%	No. of Bacteria	%	No. of Bacteria	%	No. of Bacteria	%
0	1,023	100	1,511	100	73	100	116	100	3,082	100	3,485	100
3	231	22	507	33	17	23	72	62	820	27	930	27
6	135	13	298	19	9	12	50	43	417	16	548	16
10	179	7	81	17	3	4	35	30	245	8	305	9
15	84	5	65	6	2	3	12	9	151	5	250	8

Allen [4a] believes bacterial vegetations occur selectively at the sites of greatest impact on contraction of the heart and contact with the blood stream. Nedzel [1] found endothelial damage of the valvular endocardium following the injection of a pressor substance and decided that these lesions were due to mechanical trauma at the sites of greatest contact during the pressor episodes. These lesions were demonstrable in some instances one hour after the injection of vasopressin and were

4. (*a*) Allen, A. C.: A Case of Bacterial Endocarditis Illustrating the Mechanism of Localization and the Nature of Vegetations, Am. Heart J. **21**:667-675, 1941. (*b*) Keefer, C. S.: The Pathogenesis of Bacterial Endocarditis, ibid. **19**:352-363, 1940. (*c*) Willius, F. A.: Subacute Bacterial Endocarditis: Pathogenesis, Proc. Staff Meet., Mayo Clin. **19**:431-435, 1944. (*d*) Kinsella, R. A., and Muether, R. O.: Experimental Streptococcic Endocarditis, Arch. Int. Med. **62**:247-270, 1938.

5. Rosenow, E. C.: Experimental Infectious Endocarditis, J. Infect. Dis. **11**:210-224, 1912.

6. Wadsworth, A. B.: A Study of the Endocardial Lesions Developing During Pneumococcus Infection in Horses, J. M. Res. **39**:279-292, 1919.

7. Dick, G. F., and Schwartz, W. B.: Experimental Endocarditis of Dogs, Arch. Path. **42**: 159-162, 1946.

8. Blahd, M.; Frank, I., and Saphir, O.: Experimental Endocarditis in Dogs, Arch. Path. **27**:424-432, 1939.

characterized by subendocardial hemorrhages of the valve leaflets with edema of the cusps. Intravenous injection of bacteria was followed by deposition of bacteria into the areas of damage. Nedzel [1] believed these areas of endocardial damage to be a prerequisite for the development of bacterial endocarditis.

In our experiments, valvular lesions in dogs have been demonstrated with large arteriovenous fistulae which are grossly and microscopically similar to those reported by Nedzel.[1] These lesions are acute, occurring within six hours after the production of the fistulae. Increased cardiac load and force of cardiac contraction seems to be the best explanation for the occurrence of these lesions. They occurred at the sites where trauma is most likely to occur, i. e., on the mitral leaflets, chordae tendineae, and papillary muscles. It is possible that these endocardial lesions again create a likely focus for the deposition of the bacteria which are constantly entering the blood stream.

In dogs having large arteriovenous shunts, Lillehei and co-workers [2] were able to demonstrate bacterial vegetations either on the valves or in the shunts. Spontaneous bacteremias developed in two dogs in our series, but no bacterial valvular vegetations were demonstrable. However, in the regions of the shunts a marked inflammatory reaction, mostly localized about the silk suture material, was found, and cocci were seen scattered throughout these sections. It is possible that these areas served as foci for bacteria entering the general circulation.

In the normal animal, bacteria introduced into the blood stream are rapidly removed in the splanchnic circulation. In animals with a large arteriovenous fistula, the extent of removal in the splanchnic systems remains the same; however, the rapidity with which bacteria are removed from the blood stream is diminished. The latter would seem to be due to the number of times the blood can pass through the splanchnic viscera where an efficient removal system exists. It would appear that in the presence of large arteriovenous fistulae a considerable volume of blood bypasses the splanchnic circulation in its rapid passage through the fistula; thus the clearance of the blood stream of invading bacteria would be slowed.

SUMMARY

1. Large arteriovenous fistulae produced immediate (six hours) and prominent endocardial damage.

2. The circulatory disturbance produced by these fistulae slowed the rate at which the blood stream was cleared of bacteria.

3. This circulatory disturbance did not produce a change in the extent of removal of bacteria from the splanchnic viscera (liver and spleen).

SIMPLE METHOD OF CUTTING FULL-THICKNESS SKIN GRAFTS OF ALL SIZES AND SHAPES

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THE FREE transplantation of full-thickness skin grafts has the advantage over the tubed and pedicle flap method in that it saves much time in the course of operative treatment. This method of free transplantation is indicated in cases in which all conditions are aseptic and in which the stuffing of unnecessary subcutaneous fat is not desired. Thiersch and Reverdin grafts can be used without hesitation on clean granulating areas, but full-thickness grafts can be used only on aseptic and even surfaces of host tissue. The main advantages of the full-thickness grafts over Thiersch and Reverdin grafts are that they have good functional and resistance powers and produce excellent cosmetic results. The greater the thickness of the graft, the less will be the changes in pigmentation.

One may say that there is danger of necrosis in the use of free full-thickness grafts, but this could be avoided by proper technique and also by not taking subcutaneous fat along with the skin. The full-thickness grafts were known to the German surgeons as Krause flaps. But transplantation of Krause grafts was not used extensively through fear of necrosis. When German surgeons came to know of the widespread use of free skin grafting in America, especially of grafts removed by the use of dermatomes, it gave a new impetus to us in reviving our methods of free skin grafting. During the hard times we were not in a position to purchase such expensive apparatus and were compelled to devise the method which will be described.

It should be mentioned that this technique was thought of not only from the point of view of avoiding the purchase of costly apparatus but also of taking into consideration the surgical advantages gained from it.

Every method or technique has its advantages and disadvantages. The disadvantages of the technique which is to be described are that one cannot ensure accurate mathematical precision in the thickness of the graft as with the use of the dermatome. It also involves more time. The disadvantages of the dermatome are that the dimensions of the flap are limited (maximum dimension being 10 by 20 cm.) and the shape of the flap is rectangular. Consequently many flaps are needed, and also certain parts must be discarded when one has to use these flaps to cover large areas and areas which are irregular in shape. Therefore the cutting of full-thickness grafts with the technique that is to be described has the main advantage of getting them into any size and form which is actually needed. The technique of this simple method is as follows:

A sterile piece of linen is taken and pressed against the host tissue in order to get an imprint of the area of the defect. The imprint on the linen is cut out with

From the University Surgical Clinic (Director, Prof. Hans Hellner, M.D.).

a pair of scissors and then placed over the area from which the graft has to be taken. An incision is made all around the pattern of linen, not exactly touching the border but one-tenth greater than the pattern, thus allowing for a slight shrinkage of the skin. The usual shrinkage is one-third of the original dimensions, but in order to allow the lymph spaces to be open one-tenth more of the area is sufficient; thus the flap when sutured in is under slight tension.

An autoclaved round wooden ruler or rod (about 4 cm. in diameter and 40 cm. in length) over which a piece of linen is tightly rolled and kept in position with

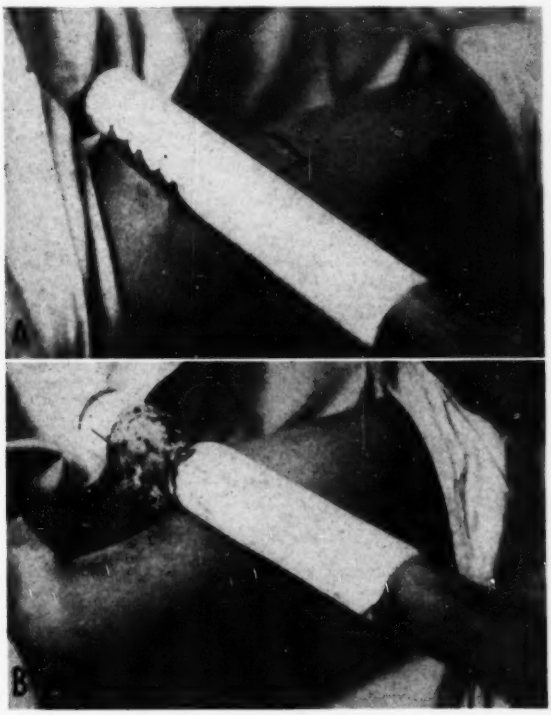

Fig. 1.—*A*, one edge of the flap sutured onto the linen rolled up on the rod. *B*, process of cutting flap with rod rolled up on tension. (By this means scalpel could be used on proper layer, thus avoiding subcutaneous fat.) At this stage, sides of flap are sutured to linen with single stitches in order to prevent transverse shrinkage.

small nails is placed at the narrow end of the flap. The narrow end of the flap is now sutured onto the linen on the rod by means of fine interrupted silk stitches (Fig. 1). The rod is gradually rolled up, thus giving a pull upward on the skin. Thereby one could easily see the underlying fat adhering to the skin and thus cutting the flap at a proper level (between dermis and fat) avoiding the subcutaneous fat (Fig. 2). At the end of each full turn of the rod the sides of the skin flap should be sutured to the linen with single stitches in order to avoid shrinkage in breadth (Fig.1). It may be mentioned here that the linen used for the pattern may be left

Fig. 2.—Microscopic section of a skin flap, giving some idea of the thickness used in the described technique.

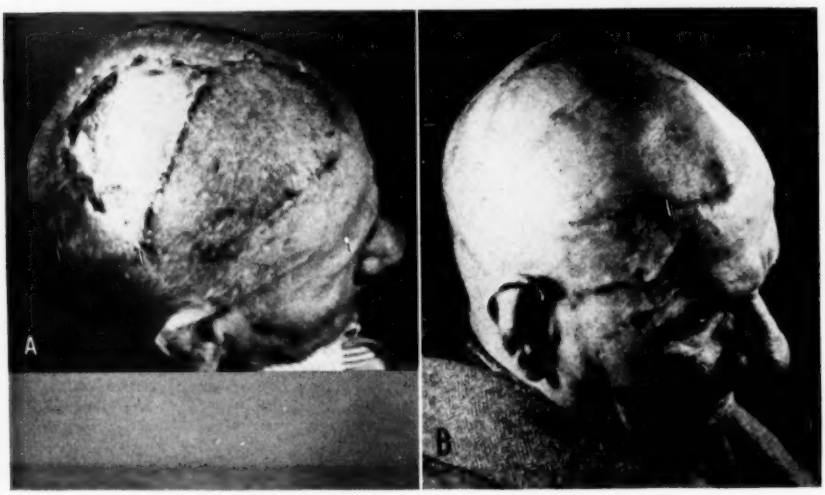

Fig. 3.—*A*, residuum of carcinoma of scalp involving the bone. After radical extirpation (including bone) a pedicle flap from neighboring side was moved up. In area from which pedicle flap was taken, a full-thickness skin graft was successfully implanted, 2 weeks postoperatively. *B*, result one year postoperatively.

Fig. 4.—*A*, 12-year-old girl with extensive keloid scars resulting from burns received at the age of 5 years. Masses of keloids extended all over the upper part of the chest from one shoulder to the other. She was therefore unable to brace her shoulders back and also had difficulty in inspiration. This operation was considered not only for cosmetic reasons but also, mainly, for the purpose of functional improvement. *B*, great masses of keloid removed and implantation of one oval full-thickness skin graft (20 by 35 cm.). *C*, total healing of graft three months after operation before pigment is assimilated. At this stage the patient is able to brace her shoulders back easily. Minor corrective operations are planned.

Fig. 5.—*A*, extensive keloids with painful relapsing ulcers in right hand caused by burns. The patient was unable to stretch the fingers sideways. *B*, hand after excision of scars (including the interdigital folds) and transplantation of a somewhat heart-shaped full-thickness graft immediately thereafter. *C*, *D*, highly satisfactory functional and cosmetic end-result. Note enlarged first interdigital fold.

Fig. 6.—Bilateral syndactylism (third and fourth fingers) in a 6-year-old girl. In the left hand the fingers were separated only by cutting through the bridge of soft tissue and the area was sutured in with a single rather long full-thickness graft. Right hand was operated on according to the usual Zeller method. Note cosmetic and functional result on the left hand two years after operation. It should be mentioned that when the Zeller method is used a plaster usually has to be worn for several weeks in order to avert contracture of fingers; whereas in the operative method used on the left hand, no contracture prophylaxis is necessary. Because of the above-mentioned advantages, we resort to the full-thickness graft method in all our cases of syndactylism.

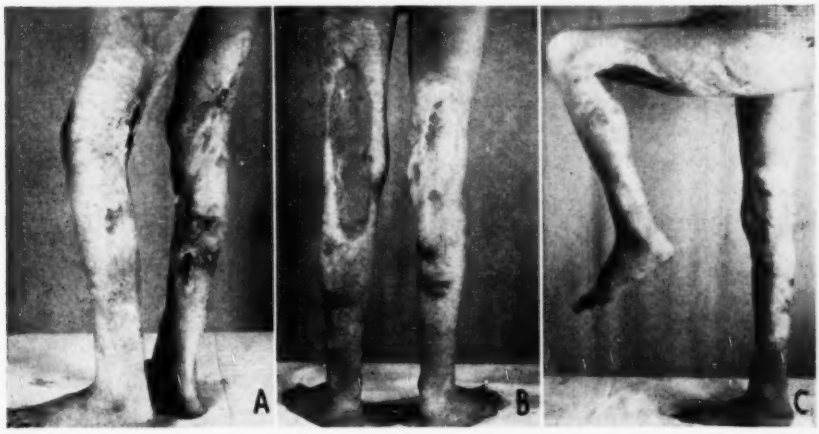

Fig. 7.—*A*, leg of a 10-year-old boy, with a pterygoid-shaped scar of 5 years' duration on the flexor side of the left knee, caused by burns due to an explosion. Patient was unable to have full extension of the knee. Because of permanent ulcers on the scar, it was thought inadvisable to perform a Z-plasty. *B*, and *C*, transplanted flap (15 by 30 cm.) healed after excision of the scar. This stage is completed six months after operation, and now full extension and flexion of the knee is possible.

Fig. 8.—Foot of a 14-year-old boy who for five years had had an extremely painful scar over the instep as a result of pressure of a very tight plaster cast. Illustration shows full-thickness skin graft implanted and healed after excision of the scar; stage is two months after operation. Patient has no pain now even while wearing shoes.

in place while the skin is being rolled up so that the raw surface will not touch the superficial skin, as a precaution for asepsis.

It is self-evident that the host area is kept free of the slightest bleeding. When the suturing in is completed (Fig. 5*B*) a piece of gauze with penicillin ointment is spread over the entire area and over this a flat piece of rubber sponge is placed and bandaged in place with slight and uniform pressure. This region of the body should be absolutely immobilized for two weeks. Penicillin may be administered parenterally in prophylactic doses.

The theoretical objection to this technique is that the cells would be damaged by overstretching the skin when it is rolled upward. But in practice it has been shown that such damage does not occur. All such operations done in our clinic, whether great or small flap transplantations, have proved successful.

The raw surface from which the flap was removed is treated by excising the subcutaneous fat and mobilizing the skin all around by blunt dissection and bringing the skin margins together and suturing them. This has an advantage over self-epithelization of quicker healing and giving better cosmetic results.

A few cases are cited in the legends of the illustrations to show the success of this method.

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TECHNIQUES AND RADIATION PRECAUTIONS FOR INTRATUMOR INJECTIONS WITH RADIOACTIVE COLLOIDAL GOLD

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INTRATUMOR injection of radioactive colloidal gold as a means of sharply localizing radiation within tumors was proposed in 1947 by P. F. Hahn.[1] Perhaps the main reason that widespread clinical use has not yet been made of this form of therapy is the technical difficulty of (1) insuring an even dispersion of the radioactive solution throughout the tumor, and (2) preventing the therapist from receiving hazardous amounts of radiation when he is working with high levels of activity. These technical problems can largely be overcome by use of the special equipment and techniques which are described in this paper.

PHYSICAL PROPERTIES OF Au^{198}

Au^{198} is produced from the stable isotope Au^{197} by neutron bombardment in the chain-reacting pile at Oak Ridge. Since Au^{197} has a high cross section capture for neutrons (100 barns), the production of Au^{198} is reasonably efficient, and a high specific activity can be attained. The average specific activity at the time of processing is 3.4 mc. per milligram.[2]

$$Au^{197}\ (n, \gamma)\ Au^{198}$$

$$Au^{198} \xrightarrow{T/2\ =\ 2.7\ d.} Hg^{198} + \beta\ (0.97\ mev) + \gamma\ (0.41\ mev)$$

The isotope thus produced has a half-life of 2.7 days. Approximately 95% of the ionization produced is due to beta rays (0.97 mev) while only 5% is due to

From the Laboratories and Surgical Service of the Peter Bent Brigham Hospital and the Harvard Medical School.

This work has received support from the Atomic Energy Commission, from the American Cancer Society through an institutional grant to the Harvard Medical School, and from a grant from the American Cancer Society (Massachusetts Division), Inc.

Dr. F. D. Moore, Moseley Professor of Surgery at Harvard Medical School gave encouragement and advice throughout this work. Drs. Wheeler, Rubenstein, and Coleman carried out this investigation as a part of their undergraduate work in surgery at the Harvard Medical School. The apparatus described was constructed by Mr. F. C. Christenson at the Machine Shop of the Harvard Medical School.

1. Hahn, P. F.; Goodell, J. P. B.; Sheppard, C. W.; Cannon, R. O., and Francis, H. C.: Direct Infiltration of Radioactive Isotopes as a Means of Delivering Ionizing Radiation to Discrete Tissues, J. Lab. & Clin. Med. **32**:1442-1453, 1947.

2. Gleason, G. I., and Tabern, D. L.: Preliminary Manual of the Properties and Uses of Colloidal $Gold^{198}$, North Chicago, Ill., Abbott Laboratories, 1951.

gamma rays (0.41 mev). Since the maximum range of the beta particles is 3.8 mm. in water,[3] it can readily be seen that the greater part of the ionization produced by this isotope occurs in the area immediately around the source.

As supplied,[4] the colloidal solution is sterile, pyrogen free, and stable on autoclaving or on mixture with isotonic dextrose or sodium chloride solution. Each cubic centimeter of solution contains 2×10^{12} particles which are roughly 0.060 μ in diameter.[5] The specific activity at the time of shipment varies between 20 and 30 mc. per milliliter.

EQUIPMENT

Before technically satisfactory injections of radioactive colloidal gold could be made with safety, it was necessary to design equipment which would (1) insure adequate protection against radiation hazards, (2) permit the accurate delivery of small volumes of fluid, and (3) remain light and flexible enough to be used deep in a surgical field. Equipment was therefore constructed in which the bulk of the solution was placed in a lead container near the operative site, and the fluid was conveyed to the tumor through fine-caliber polyvinylene tubing[6] (internal diameter 0.8 mm.; volume 0.15 ml. per foot). Such tubing can be easily maneuvered by the surgeon and yet is not hazardous since it contains only a small amount of fluid at any given time. Beta radiation is eliminated by passing the plastic tubing through rubber pressure tubing whose walls are 0.7 cm. thick. Figures 1 and 2 show the equipment used for injection; and Figure 3 shows the lead pot in which the isotope is stored. Using this equipment it is possible to carry out all the steps of an intratumor injection without ever handling the isotope directly.

TECHNIQUES

A. Use of the Lead-Shielded Syringe.—Before operation the sterile parts of the equipment—a syringe, a clip which fits over the syringe, plastic tubing, rubber pressure tubing, needles, and Kelly clamps (Figs. 1 and 2) are all assembled in the way in which they will be used, so that at operation the complete set is ready for use without further handling being necessary.

The fluid is withdrawn from the bottle held in the lead pot (Fig. 3) directly into the lead-shielded syringe (Fig. 1) after a short needle has been inserted through the rubber cap of the original container to keep the air in the bottle at atmospheric pressure. When enough radioactive gold for the operation at hand has been withdrawn, the platform which holds the lead shield is rotated through a 90-degree angle and clamped in place. This permits bubbles to rise to the top of the syringe, where they can be removed by turning the dial pointer which controls the plunger. In order to inject into any given area the surgeon inserts the needle

3. Marinelli, L. D.; Quimby, E. H., and Hine, G. J.: Dosage Determination with Radioactive Isotopes: II. Practical Considerations in Therapy and Protection, Am. J. Roentgenol. **59**:260-281, 1948.

4. Radioactive colloidal gold may be obtained commercially from Abbott Laboratories, North Chicago, Ill., by investigators with allocations from the Atomic Energy Commission. Address inquiries to Dr. D. L. Tabern, Head, Special Research.

5. Hahn, P. F.: A Manual of Artificial Radioisotope Therapy, New York, Academic Press, 1951, Chap. 9.

6. Polyvinylene tubing can be obtained from the Irvington Varnish and Insulator Co., Irvington, N. J.

to the position desired, and his assistant turns the dial pointer the number of scale divisions required to deliver the proper volume. The surgeon then waits 10 seconds so that the fluid has a chance to diffuse and hence will not tend to leak back from the injection site. This process is repeated until the surgeon feels the tumor has had adequate injection.

B. Calculation of the Volume to Be Injected.—Before the actual injection of colloidal Au^{198} is begun, it is necessary to determine the number of separate injections to be made and the volume of each injection. These figures are based on the size of the tumor and on the number of equivalent roentgens [7] to be delivered to it. The size of the tumor is determined at operation by measuring its dimensions and

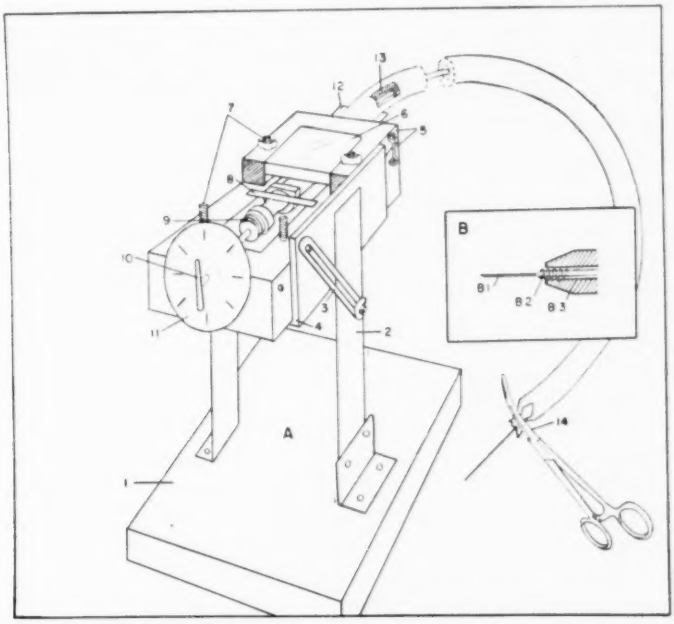

Fig. 1.—*A*, diagrammatic representation of lead-shielded syringe and tubing which carries fluid from syringe to injection needle: (*1*) baseboard; (*2*) metal supports; (*3*) adjustable slide; (*4*) platform for lead case; (*5*) lead case and cover; (*6*) glass window; (*7*) set screws with wing nuts; (*8*) removable metal bar; (*9*) brass coupling between syringe plunger and injection screw; (*10*) dial pointer; (*11*) dial; (*12*) brass support; (*13*) pressure tubing window, polyvinylene tubing; (*14*) Kelly clamp. *B*, detail of attachment between injection needle and plastic tubing: (*B 1*) 22 G needle shaft (4, 8, 12 cm. lengths); (*B 2*) No. 32 stainless steel wire; (*B 3*) tapered rubber pressure tubing.

computing the volume from these measurements. Since the calculation of dosage must be based on weight, the volume (in cubic centimeters) is assumed to be roughly equal to the weight (in grams). The choice of the proper number of equivalent roentgens to be delivered is made prior to operation and is determined

7. An equivalent roentgen (abbreviated e. r.) is "that amount of beta radiation which, under equilibrium conditions, releases in one gram of air as much energy as one roentgen of gamma rays." [3]

by factors described elsewhere.[8] When the approximate weight of the tumor and the number of equivalent roentgens to be delivered are known, the number of millicuries which must be injected can then be calculated from the formula $D\beta - 76$ C e. r., where $D\beta$ represents the dosage delivered by beta radiation and C represents the concentration of activity in the tumor in terms of millicuries per kilogram.[8] To simplify this calculation during the operation, it has been found helpful to use tables on which are recorded the number of millicuries required to

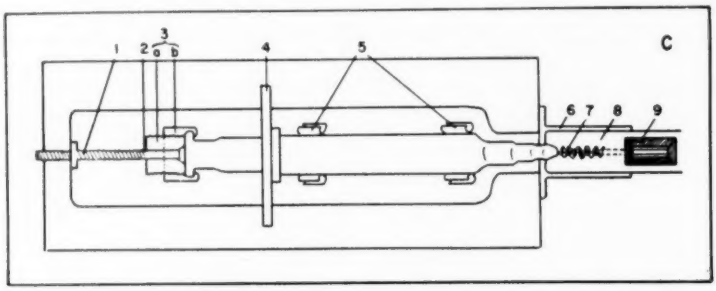

Fig. 2.—Diagrammatic representation of lead case with cover removed and syringe in place: (*1*) screw between dial pointer and syringe plunger; (*2*) end of threads (screw head revolves freely); (*3*) brass screws; (*4*) removable metal bar; (*5*) metal clips; (*6*) brass support; (*7*) wire around plastic tubing; (*8*) pressure tubing; (*9*) pressure tubing window.

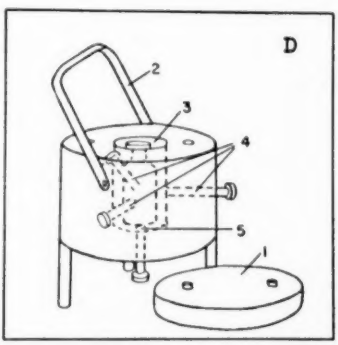

Fig. 3.—Schematic diagram of lead pot in which colloidal Au^{198} is stored: (*1*) lead cover; (*2*) metal handle; (*3*) chamber for Au^{198} bottle; (*4*) clamping screws; (*5*) elevating screw.

deliver various amounts of radiation to any given tumor volume. In order to convert the required number of millicuries into the appropriate volume it is necessary to divide the total number of millicuries to be injected by the number of millicuries in each milliliter of solution. This volume is then given in divided doses of as many separate injections as the surgeon thinks indicated.

8. Wheeler, H. B.; Botsford, T. W.; Rubenstein, J. H.; Coleman, M. D., and Moore, F. D.: Treatment of Inoperable Neoplasms by Intratumor Injection of Radioactive Colloidal Gold: A Preliminary Report, to be published.

For example, let us assume the surgeon wishes to deliver 25,000 e. r. to a roughly spherical tumor mass with a mean diameter of 5 cm. Looking at a table he sees that a tumor with this diameter has a mass of about 66 gm., and a second table shows that to deliver 25,000 e. r. to a mass of this size requires 21.7 mc. of radioactive colloidal gold. Assuming a specific activity of 10 mc. per milliliter at the time of injection, this means that 2.17 ml. of the solution on hand must be used. If the surgeon wishes to distribute 100 separate point sources of radiation throughout the tumor, then his assistant delivers 0.0217 ml. for each injection. (In actual practice the volume delivered would be 0.0212 ml., since this is the amount delivered by two scale divisions, and it is customary to use the closest convenient figures because the determination of dosage is not precise enough to warrant meticulous accuracy in the volume injected.)

C. Distribution of Radioactivity Throughout the Tumor.—The most difficult technical problems of the entire procedure is the even dispersion of radioactivity throughout the tumor. We believe that the degree of dispersion achieved is roughly proportional to the degree to which certain principles are followed:

1. The volume of fluid injected should closely approach the maximum volume which the tumor is capable of retaining.
2. A large number of separate injections should be made.
3. The tumor must be adequately exposed.
4. The surgeon must have some definite plan of injection dictated by the configuration of the tumor.

At present we use one of three techniques for spacing injections throughout a tumor. The first of these is the use of a lucite block with geometrically spaced holes through which injections can be made. This block is thick enough to prevent any lateral motion of the needle, and its use permits the production of parallel paths of injection which traverse the substance of the tumor at precisely spaced distances from each other. The second method is the use of wide-meshed paraffin gauze which can be molded over irregular tumors and which is marked off in one centimeter squares that serve as guides for spacing the sites of injection. The last method is free-hand injection into tumor masses which are so shaped or so situated as to render the first two methods technically unsatisfactory. Even this mechanically unaided method has some degree of precision since a definite plan of injection based on the shape of the individual tumor is followed in every case. The exact method of injection followed in different types of tumors will be described elsewhere.[8]

RADIATION HAZARD TO PERSONNEL

Various methods have been used to assess the radiation hazard to surgeon, patient, and nursing personnel. The data obtained by these methods have consistently shown less exposure to radiation than the limits of tolerance[9] (Table). Film badges worn over the upper thorax have never shown any exposure to radiation when the equipment and techniques previously described were in use. During four operations badges were placed in the glove of the person most directly concerned with handling the isotope. None of these badges recorded any exposure to radiation.

9. As defined at the Permissible Doses Conference of the radiation protection committees of the United States, Great Britain, and Canada, held at Chalk River, Ont., Canada, Sept. 29-30, 1949.

Victoreen pen ionization chambers were used during the first few operations and also failed to reveal any appreciable degree of activity.

Levels of Maximum Permissible Exposure to Various Parts of the Body as Recommended by the Chalk River Conference (1949)

	Rep per Week of Beta Radiation
In working area or in body organs excepting epidermis, hands, and forearms	0.3
At body surface or epidermis	0.5
On the surface or in the epidermis of hands and forearms	1.5

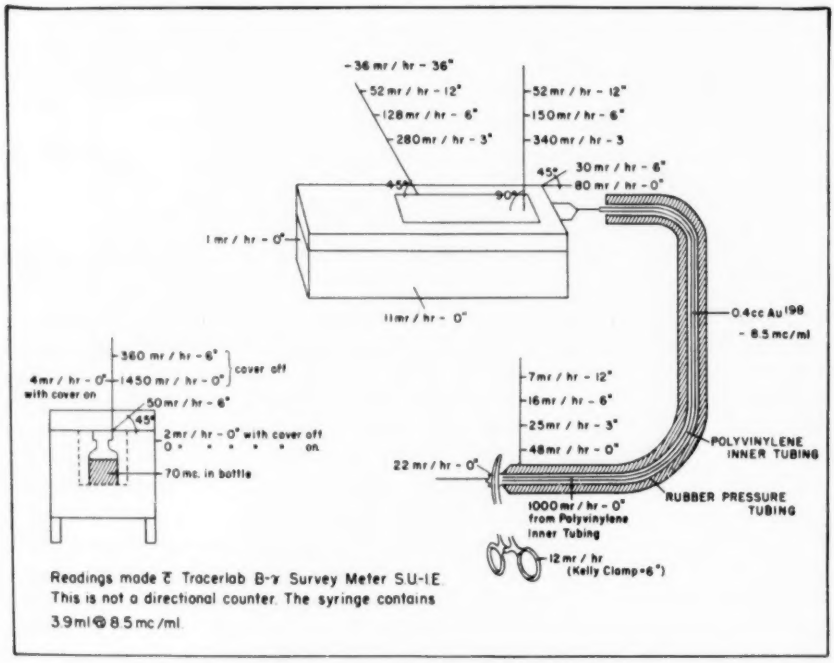
36 mr / hr - 36"
52 mr / hr - 12"
128 mr / hr - 6"
280 mr / hr - 3"
52 mr / hr - 12"
150 mr / hr - 6"
340 mr / hr - 3
45°
30 mr / hr - 6"
80 mr / hr - 0"
90°
1 mr / hr - 0"
11 mr / hr - 0"
0.4 cc Au 198
- 8.5 mc/ml
360 mr / hr - 6"
4 mr / hr - 0" with cover on
1450 mr / hr - 0"
cover off
50 mr / hr - 6"
45°
2 mr / hr - 0" with cover off
0 " " " " on
70 mc. in bottle
7 mr / hr - 12"
16 mr / hr - 6"
25 mr / hr - 3"
48 mr / hr - 0"
22 mr / hr - 0"
POLYVINYLENE INNER TUBING
RUBBER PRESSURE TUBING
1000 mr / hr - 0" from Polyvinylene Inner Tubing
12 mr / hr (Kelly Clamp +6")
Readings made with Tracerlab B-γ Survey Meter SU-1E
This is not a directional counter. The syringe contains
3.9 ml @ 8.5 mc/ml

Fig. 4.—Schematic representation of monitoring values obtained on a typical set-up used for injection.

Figure 4 is a diagrammatic representation of typical monitoring data obtained on a set-up actually used for injection. Perhaps the most important points brought out by the diagram are the facts that the reading at the point where the surgeon's hand grasps the Kelly clamp is 0.012 r per hr. and the reading at the point where the assistant's hand turns the injection screw is 0.001 r per hr. Monitoring of the rest of the equipment reveals relatively small amounts of radiation which decrease rapidly with distance. The highest readings are obtained immediately over the glass window in the lead brick. Here with a typical amount of activity in the syringe (33 mc.) the monitoring values at 3 in. (7.6 cm.) are 0.34 r per hr. and at 12 in. (30.5 cm.) are 0.05 r per hr.

Colloidal gold is a watery liquid with a deep purple color, which is readily identified should there be any contamination of the field, sponges, or instruments. Monitoring of contaminated equipment has failed to show any appreciable radiation hazard, but such equipment is routinely stored in a locked room until its activity has decayed.

Postoperatively the patients' urine and feces have never shown any appreciable radioactivity. Monitoring of the wound surface itself, however, has revealed up to 0.25 r per hr. (following an intra-abdominal injection of 55 mc). The readings at 3 ft. (91.4 cm.; arbitrarily considered nursing distance) have never exceeded 0.03 r per hr.

No patient has shown any hematopoietic changes or liver damage which could be measured by routine laboratory procedures. Intravenous injection of a large dose of radioactive colloidal gold into dogs has been shown to produce only moderate hematologic responses such as would be expected from any form of ionizing radiation.[10]

As of this writing we have used radioactive colloidal gold on 22 occasions to treat 12 different patients. The clinical response and histological changes observed in these patients are now being summarized for presentation together with a discussion of the indications, dosage levels, and future role of such therapy.[8]

SUMMARY

It is possible to localize radiation within tumors by the direct intratumor injection of radioactive colloidal gold.

Methods and equipment are described which permit the dispersion of a calculated dose of this isotope within a tumor with minimal radiation hazard to surgeon, patient, and nursing personnel.

ADDENUM

Since this manuscript was submitted for publication, an article dealing with the handling of radioactive gold for therapeutic purposes has been published elsewhere by M. Ter-Pogossian and A. I. Sherman.[11] It deals with many of the problems discussed in this paper and is recommended as further reading for persons interested in this field.

10. Wheeler, H. B.; Jackson, M. A., and Hahn, P. F.: Hematology of the Dog Following Intravenous Administration of Radioactive Colloidal Gold, Am. J. Physiol. **166**, 2:323-327, 1951.

11. Ter-Pogossian, M., and Sherman, A. I.: Handling of Radioactive Gold for Therapeutic Purposes, Nucleonics **10**(No. 3):23-27, 1952.

CARCINOMA OF THE PANCREAS

Symptoms, Signs, and Results of Treatment in One Hundred Twenty-Two Cases

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DEFINITIVE surgical resection of carcinoma of the head of the pancreas or papilla of Vater is relatively recent [1] and has been performed so infrequently that the proper evaluation of its place in treatment is difficult. The over-all results of treatment of carcinoma of the pancreas are even more difficult to establish, since most reported series include only cases with resection. Recent reviews by Loggan and Kleinsasser [2] and Child [3] make redundant a further complete review of the literature.

The incidence of carcinoma of the pancreas is not rare, as established from the 1949 figures of the Connecticut State Tumor Registry.[4] It occurred 104 times in 4,661 registered cases, an incidence of 2.2%. The incidence in males was higher, 2.8%, as compared with 1.7% in women. This male-female ratio of 1.6 : 1 compares with the 2 : 1 and the 2.5 : 1 ratio in postmortem series.[5] All patients were over 35 years of age, and 91.6% were over 55 years of age. It is of interest that of the 104 patients only 4 were subjected to radical surgery, although in 31 the carcinoma was reported as being localized at the time of diagnosis.

From the Tumor Registry of the Section of Oncology of the Department of Surgery, Yale University School of Medicine.

Dr. Cliffton is Assistant Professor of Surgery (Oncology) Yale University School of Medicine.

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1. Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, Ann. Surg. **102**:763-779, 1935.

2. Loggan, P. B., and Kleinsasser, L. J.: Surgery of the Pancreas: the Result of Pancreaticoduodenal Resections Reported in the Literature, Int. Abst. Surg. **93**:521-543, 1951, in Surg., Gynec. & Obst., Dec., 1951.

3. Child, C. G.; Holswade, G. R.; McClure, R. D., Jr.; Gore, A. L., and O'Neill, E. A.: Pancreatoduodenectomy with Resection of the Portal Vein in the Macaca Mulatta Monkey and Man, Surg., Gynec. & Obst. **94**:31-45, 1952.

4. Furnished by the Tumor Register of Division of Cancer and Other Chronic Diseases, Connecticut State Board of Health.

5. (*a*) Mikal, S., and Campbell, A. J. A.: Carcinoma of the Pancreas: Diagnostic and Operative Criteria Based on 100 Consecutive Autopsies, Surgery **28**:963-969, 1950. (*b*) Miller, J. R.; Baggenstoss, A. H., and Comfort, M. W.: Carcinoma of the Pancreas: Effect of Histological Type and Grade of Malignancy on Its Behaviour, Cancer **4**:233-241, 1951.

Three factors seem to be of prime importance in the poor results of treatment to date: (1) the failure of early diagnosis, (2) the high mortality of the radical surgical approach, and (3) the combined factor of difficulty in operative diagnosis and the frequency of explorations made with a preoperative diagnosis of common duct stone by surgeons unfamiliar with the procedure of pancreatectomy. Little has been achieved to improve the mortality, and from a review of the surgical literature one would judge that the mortality has remained high, probably because of efforts to increase the extent of the surgery with more complete resection, including segments of the portal vein and superior mesenteric veins, or by total pancreatectomy.[6]

The feeling that resection for carcinoma of the head of the pancreas should be abandoned has seemed to gain momentum recently because of the poor results in the hands of the average surgeon, supported, no doubt, by soul-searching questions by outstanding surgeons.[7] Inherent in this problem are several factors which could be and possibly have been misinterpreted. Most surgeons with a large experience have separated their cases into those with carcinoma of the head of the pancreas, carcinoma of the ampulla of Vater, and carcinoma of the duodenum, and others have gone so far as to differentiate carcinoma arising in the common duct or pancreatic duct within the head of the pancreas from other carcinomas of the head of the pancreas. Most of these differentiations have undoubtedly been made on the basis of pathological examination following resection. They therefore can be of little value to the general practitioner, internist, or surgeon attempting to make a diagnosis, or to the surgeon with or without a positive biopsy attempting to come to a decision for or against radical surgery. Indeed, the pathologist himself may at times have difficulty in deciding the originating site in a malignant tumor involving pancreatic tissue and duodenal wall. At necropsy carcinomas of the head of the pancreas are frequently found to invade and cause malignant ulceration of the duodenal mucosa (24% in one necropsy series [5a]).

Actually, the results of definitive surgery for carcinoma of the head of the pancreas are not much worse than the results of resection for carcinoma of other sites where there is greater experience, more specialization, and perhaps better methods of early diagnosis. There may be much wrong with the approach to diagnosis and therapy, but no improvement will follow the dropping of the best method available at present for handling this very desperate medical and surgical problem.

A review of the cases with diagnoses of carcinoma of the pancreas in our own institution with the idea of answering some of the questions brought up by others and in our own minds seemed desirable. This is a small group of cases, but one that has been rather completely studied and carefully followed.

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6. (*a*) Moore, G. E.; Sako, Y., and Thomas, L. B.: Radical Pancreaticoduodenectomy with Resection and Re-Anastomosis of the Superior Mesenteric Vein, Surgery **30**:550-553, 1951. (*b*) Greenfield, J., and Sanders, J. H.: Total Pancreatectomy with Report of Post-Operative Physiologic Studies, Surgery **25**:824-838, 1949. (*c*) Child, Holswade, McClure, Gore, and O'Neill.[3]

7. Cattell, R. B., and Pyrtek, L. J.: An Appraisal of Pancreatoduodenal Resection: A Follow-Up Study of 61 Cases, Ann. Surg. **129**:840-849, 1949. Whipple, A. O.: A Discussion of the Lesions of the Pancreas Amenable to Surgery, J. Mt. Sinai Hosp. **15**:123-131, 1948. Parsons, W. B.: Carcinoma of the Pancreas and Carcinoma of the Ampulla of Vater: A Re-Evaluation, Bull. New York Acad. Med. **27**:339-345, 1951.

MATERIAL

Of the 135 cases of malignant tumor of the pancreas, ampulla of Vater, common duct, or duodenum registered in the Tumor Registry of Yale University since 1923, 122 were cases of carcinoma of the pancreas, of the common or pancreatic duct within the head of the pancreas or of the ampulla of Vater. Cases of nesidioblastoma (islet-cell tumor) and of carcinoma of the duodenum are not included in these 122 cases. In only 75 of the 122 was the diagnosis pathologically proved, and in 20 of the 75 the diagnosis was made only at autopsy; the majority of the latter were cases of carcinoma of the body or tail of the pancreas.

PREDOMINANT SYMPTOMS

Is carcinoma of the pancreas a silent (i. e., painless) lesion, as commonly supposed? This has been shown to be untrue in many previous studies.[8] Berk [9] stated

TABLE 1.—*Duration of Symptoms*

	1st Symptom to Definitive Treatment	1st Symptom to 1st Physician Visit
No delay	0	29
< 1 mo.	12	8
1-2 mo.	10	8
2-3 mo.	12	7
3-4 mo.	20	4
4-5 mo.	5	2
5-6 mo.	8	1
6-7 mo.	10	2
7-8 mo.	2	..
8-9 mo.	7	..
9-10 mo.	4	1
10-12 mo.	3	1
> 12 mo.	10	..
Undetermined	19	59
Total	122	122

that pain was the first symptom in 50% of 849 collected cases and in 86.1% of his personally controlled cases. He described very carefully the rather specific type of pain. Drapiewski [10] has offered a satisfactory pathological explanation in the invasion of nerves by tumor.

Of the 122 cases in this series, an accurate estimate of the onset of symptoms could be made in 113. In Table 1 it will be seen that only 34 patients had symptoms referable to the lesion for less than three months, and 18 had had symptoms for more than a year. That these symptoms were real is confirmed by the early visit to a physician by those 63 patients from whom the information was obtained (Table 1). Twenty-nine visited their physician immediately, and 54, or 85%, visited their physician within three months of the onset of their symptoms. Pain was the most frequent symptom, being absent in only 19, or 16.6%, of the patients.

8. Futcher, T. B.: Cancer of the Pancreas, Tr. A. Am. Physicians **34**:284-290, 1919. Mussey, R. D.: Pancreatic Carcinoma, M. Clin. North America **3**:681-688, 1919.

9. Berk, J. E.: Diagnosis of Carcinoma of the Pancreas, Arch. Int. Med. **68**:525-559, 1941.

10. Drapiewski, J. F.: Carcinoma of the Pancreas: Study of Neoplastic Invasion of Nerves and Its Possible Clinical Significance, Am. J. Clin. Path. **14**:549-556, 1944.

In 34, or 29.8%, pain was a complaint for more than four months before admission to the hospital for definitive treatment. Anorexia and jaundice were obviously symptoms of shorter duration (Table 2).

Significant weight loss (over 10 lb. [4.5 kg.]) had occurred before admission in 90, or 84%, of the 107 patients on whom this information was obtained. This corresponds to a figure of 90.1% showing weight loss in Eusterman and Wilbur's report.[11] In 48 of the 93 patients (50%) in whom the duration of weight loss was known, this had been observed for a period of more than three months (Table 3).

TABLE 2.—*Duration of Three Most Prominent Symptoms*

	Anorexia	Pain		Jaundice
Not stated	32	13		11
None	15	19 (16.6%)		26
1 mo.	15	20 (16.8%)		34
1-2 mo.	18	10		13
2-3 mo.	11	12		6
3-4 mo.	12	14		7
4-5 mo.	2	6		3
5-6 mo.	3	5		8
6-7 mo.	4	5	34	0
7-8 mo.	1	1	cases	0
8-9 mo.	1	3	—	0
9-12 mo.	1	3	29.8%	1
1-2 yr.	3	7		0
Over 2 yr.	4	4		1
Undetermined time	..	..		13
Noted only after admission	..	..		7

TABLE 3.—*Duration and Amount of Weight Loss*

	Number of Patients Losing					
Mo.	5 Lb.	5-10 Lb.	10-20 Lb.	20-30 Lb.	Over 30 Lb.	Unknown Amount
1	2	2	6	1	0	1
1-2	..	2	4	2	1	1
2-3	..	..	5	4	3	..
3-4	..	..	3	6	5	..
4-6	..	1	1	9	2	..
6-9	1	..	2	5	5	..
9-12	..	..	1	0	0	..
Over 1 yr.	..	..	5	3	2	10
Unknown	3	5	2	..	1	12

No weight loss, 9; weight loss undetermined, 15.

Despite these obvious signs of serious illness, jaundice was the only symptom or sign actually used in bringing patients to treatment in an operable state. Jaundice was noted in 87 of the 122 patients, and in 41 of these it was present for less than one month or was first observed after the patient's admission to the hospital. In 18 of these patients it had been noted for two or more months before definitive treatment (Table 2).

PHYSICAL EXAMINATION

The presence of clinically determined physical signs was less apparent in the physical examination records. However, it is obvious from Table 4 that an enlarged hard liver was present in over one-half of the cases (66). This finding, however, did

11. Eusterman, G. B., and Wilbur, D. L.: Primary Malignant Neoplasm of the Pancreas: A Clinical Study of 88 Verified Cases Without Jaundice, South. M. J. **26**:875-883, 1933.

not of necessity indicate inoperability, since in many instances this was due, as shown in necropsy series also, to hepatitis or ascending cholangitis.[5b] The presence of a distended gall bladder was noted in only 26 cases, although the gall bladder and the common duct were found to be distended in over 50% of the cases in which exploration was done. This figure is somewhat lower than those found in postmortem series (76 to 88%). A distinct mass in the region of the pancreas was even less frequently reported (18 times).

X-RAYS AS A DIAGNOSTIC MEANS

In the total group of 122 cases, 96 patients had adequate x-ray examinations. It is of note that of these 96 only 8 had signs, such as widening of the duodenal loop, considered diagnostic of carcinoma in the region of the head of the pancreas. None of the patients who underwent resection had such a diagnostic x-ray sign. Three of the patients on whom resection was done did have some duodenal deformity, however, and one of these was the patient who survived five years four months (Fig. 1, Case 2). Two others had evidence of extrinsic pressure on the duodenum, probably from a distended gall bladder.

TABLE 4.—*Positive Physical Findings on Abdominal Examination*

None	22
Mass in pancreas region	18
Questionable mass in pancreas region	10
Distended gall bladder	26
Enlarged hard liver	66
Distinct mass in liver	9
Ascites	4
Tenderness or resistance in upper abdomen	19

RESULTS OF TREATMENT

The total group of 122 cases have been divided, according to the type of treatment given, into five primary groups (Table 5).

Group 1.—Of the 33 cases in which the patients were not operated upon, the average survival time was five weeks, with a maximum survival of four months. In 20, or 66.6% of these, the tumors were proved by postmortem histological study to be carcinoma. Eleven of these originated in the body or tail of the pancreas and all were accompanied with generalized metastases. Four originated in the head of the pancreas, and one of these was without obvious metastases, although the patient also had an epidermoid bronchogenic carcinoma with spread to the hilar nodes. In the other five cases the point of origin within the pancreas was not definitely stated.

Group 2.—In 28 cases the patients were subjected to exploration and in 25 of these a positive pathological diagnosis was obtained either by biopsy or at postmortem examination. The postoperative mortality in this group was 19.5% and the longest survival 16 months, with an average of 3⅓ months' survival.

Group 3.—In 42 cases the patients had a sidetracking operation—cholecysto- or choledocho-gastrostomy, duodenostomy, or jejunostomy. The postoperative mor-

tality in this group of cases was 31%. In the 19 cases in which a positive pathological diagnosis was obtained, the operative mortality was 57.8%. The maximum survival in this group with pathologically proved carcinoma was 17 months, with an average of 5½ months.

Of the 122 cases in which diagnoses were made from 1923 to 1951, a sidetracking operation was done in 23 without a pathological diagnosis being obtained. In only one of these was the diagnosis obviously in error, since the patient has now survived over 15 years without evidence of tumor. The operative mortality in these 23 cases was 8.7%. Except for the one case with an incorrect diagnosis, mentioned above, the longest survival was 18 months and the average survival was approximately 7 months.

Two cases in which the patients had had sidetracking operations at other hospitals and were treated at New Haven Hospital secondarily are not included. One

TABLE 5.—*Summary of Data on 122 Patients with Diagnosis of Carcinoma of Pancreas*

	Group	No. of Cases	% of Cases	% of Operation	Postoperative Deaths (in Hospital or in 1 Mo.) No.	Postoperative Deaths (in Hospital or in 1 Mo.) %	Survival Time Maximum	Survival Time Minimum	Survival Time Average
1	**No operation**	33	27.1	....	..	....	4 mo.	30 min.	5 wk.
	No pathology	13	10.7	....	..	....	4 mo.	1 wk.	6 wk.
	Autopsy	20	16.3	....	..	....	3 mo.	30 min.	3 wk.
2	**Exploratory only**	28	22.9	31.0	5	19.5	16 mo.	1 mo.	3½ wk.
	Positive by biopsy or autopsy	25	20.4	....	5	20.0	16 mo.	1 mo.	3½ wk.
	No positive pathology	3	2.5	....	0	0	6 mo.	1 mo.	3½ wk.
3	**Sidetracking operation**	42	34.2	49.4	13	31	17 mo.	2 mo.	5.4 mo.
	No positive pathology	23	18.8	....	2	8.7	17 mo.	2½ mo.	6.8 mo.
	Positive pathology	19	15.4	....	11	57.8	10 mo.	2 mo.	3.5 mo.
4	**Resections**	13	9.8	12.6	4	33.3	Over 6 yr.	2½ mo.	2½ yr.
	Carcinoma of pancreas	12							
	one stage	8	6.6	....	3	37.4	Over 6 yr.	2½ mo.	2½ yr.
	two stage	4	3.2	....	1	25	5 yr. 4 mo.	3 mo.	2½ yr.
	Local resection	1	0.8	1.1	..	....	5 yr. 2 mo.	.....	.....
5	**Miscellaneous operations**	6	4.9	6.3	0	0	4½ mo.	2 mo.	3.6 mo.

of these the pathology of whose tumor is in doubt still survives over five years after repeated operations.

Group 4.—The 12 cases with resection will be discussed more completely later under results of treatment after 1940.

Group 5.—In six cases the patients had miscellaneous operations, including one gastroenterostomy for obstruction, four cholecystectomies, and one cholecystostomy. The average survival of these patients was 3.6 months.

RESULTS IN PERIODS BEFORE AND AFTER FIRST RESECTION

Since the first resection for carcinoma of the head of the pancreas at this hospital was performed, in 1941, the patients have been divided into two groups for special study—those seen before 1940 and those seen since 1940.

Results of Treatment in Cases with Diagnoses Before 1940.—Twenty-two pathologically proved cases of carcinoma of the pancreas or ampulla of Vater were

observed prior to 1940. One of the patients survived more than five years (G. L., Case 1). For five of the remaining 22 patients diagnoses were made only post mortem, and none had only an exploration and biopsy. Only seven had a cholecystogastrostomy or cholecystoduodenostomy. The longest survival among these patients was one year two months. The operative mortality for the 16 patients operated upon was 56%.

Results of Treatment After 1940.—From 1940 to 1951, pathological diagnoses were made in 52 cases and in 16 of these only post mortem. Eleven patients had an exploratory operation with biopsy, and 13 had sidetracking operations—cholecysto- or choledocho-gastrostomy, duodenostomy, or jejunostomy—and 1 had a gastroenterostomy. The over-all operative mortality was 36% (9 of 25 patients).

Cases with Treatment by Resection (Group 4, Table 5).—Twelve patients with carcinoma involving the head of the pancreas had resection of the head of the pancreas, duodenum, and distal stomach with choledochojejunostomy, closure of the pancreatic stump, and gastrojejunostomy. Four of these succumbed postoperatively, an operative mortality of 33.3%. On three of the four patients postmortem examinations were performed. In one, carcinoma was found in the pancreatic bed in the region of the portal vein, but in the other two no carcinoma was found. Two

TABLE 6.—*Cases 1941 to 1946 (Possible Five-Year Survivors)*

Total no. of cases	39	
Pathologically proved	27	
Resections	8	20.0% of total cases
5 year survivals	2	5.1% of total cases
		7.4% of pathologically proved cases
		25.0% of resection cases

patients, 18%, survived less than six months: One died with carcinoma in the proximal common duct; the second died suddenly, probably from a heart attack while feeling well without evidence of recurrence. One patient lived 10 months and died as a result of metabolic disturbances, including diabetes and abnormalities of fat digestion. One patient lived two years two months and then died of multiple metastases. One patient survived five years four months and then died of probable recurrence (Case 2). One patient still survives, over six years after resection, without recurrence (Case 3). Two other recent patients still survive, one over one year and the other four months after surgery. Only one patient underwent resection without a positive diagnosis of carcinoma made on pathological examination of the specimen (Case 4). Subsequent events with a recurrence of jaundice and the finding of metastatic carcinoma in the gall bladder and stump of the common duct would lead one to question the pathological diagnosis in this case rather than the surgeon's clinical impression. In retrospect, the pathologists agree that the sections show a lesion very similar to the recurrent lesion and agree that a diagnosis of carcinoma in the original specimen can be made (Fig. 4).

Of the 39 cases with treatment from 1941 to 1946, the period in which five year survivors could have appeared in the resected series, diagnoses were pathologically proved in 27. In eight resections were done, and in two of these (5.4% of the total cases, 7.4% of the cases with pathologically proved diagnoses and 25% of the cases with resection) the patients survived more than five years (Table 6).

COMMENT

The results of treatment of carcinoma in the region of the head of the pancreas in this small series of cases do not confirm the pessimistic opinion commonly held at this time.

At least four other cases of five-year survivals of patients with carcinoma of the head of the pancreas in addition to numerous cases of carcinoma of the ampulla of Vater have been reported: one of Whipple [12]; one of Miller and Clagett [13]; one of Dennis and Varco,[14] reported in the paper of Moore, Sako, and Thomas,[6a] and one case of Brunschwig.[15] Others have undoubtedly occurred and may have been reported.

The correctness of the diagnosis in the case of the patient still surviving over six years might be questioned on the basis of the ulceration of the duodenum. However, the pathological picture was that of carcinoma of the pancreas with the main mass in the pancreas and secondary invasion of the duodenum. Actually this is not uncommon, as shown by the postmortem study of Mikal and Campbell,[5a] who found this picture in 20% of their 100 cases of carcinoma of the head of the pancreas.

Diagnosis at the time of operation has been a serious problem to most surgeons.[16] In this group of cases it has apparently been successfully established either on clinical grounds or by pathologic investigations in all but two cases, and in one of these the failure was due probably to the pathologist's error rather than to that of the surgeon. However, in the past year at least one patient with a localized lesion failed to have a resection because of the surgeon's preoccupation with an absolute diagnosis. This patient should have had a good result. Several other patients in the total series with carcinomas resectable according to the description in the operative note did not undergo resection either because of the failure to obtain a positive biopsy specimen or possibly because of the pessimistic attitude concerning resection. My own experience with a first case of carcinoma of the pancreas in which a negative biopsy specimen was obtained, and in which at necropsy the tumor was still completely localized and small, deep in the gland, has led me, at least for the present, to a more radical treatment of these small tumors in the head of the pancreas.

Proper implementation of the opinion that carcinoma of the ampulla should be treated by the Whipple type resection while carcinoma of the head of the pancreas should not can only follow the surgeon's ability to distinguish these tumors without doubt. Except for those local tumors involving only the ampulla, it would seem difficult if not impossible to distinguish the two types, and I have found it impossible to distinguish them from the operative reports in this series of cases. It may be that others are able to establish the diagnosis satisfactorily before removal and careful examination.

Early duodenotomy should be helpful in distinguishing the local carcinomas of the ampulla and the duodenum or at least carcinomas that invade these sites, and

12. Whipple, A. O.: A Discussion of the Lesions of the Pancreas Amenable to Surgery, J. Mt. Sinai Hosp. **15**:123-131, 1948-1949.

13. Miller, E. M., and Clagett, O. T.: Survival 5 Years After Radical Pancreatoduodenectomy for Carcinoma of the Head of the Pancreas, Ann. Surg. **134**:1013-1017, 1951.

14. Dennis, C., and Varco, R. L.: Neoplastic Biliary Obstruction, Surgery **20**:72-81, 1946.

15. Brunschwig, A.: Results of Pancreatoduodenectomy, Cancer **2**:763-766, 1949.

16. Carlson, R. I.: The Problem of Diagnosis at the Time of Operation in Tumors of the Head of the Pancreas, Surgery **28**:672-679, 1950.

it is very helpful in making a definitive diagnosis. Actually this is not such an undesirable procedure, even if there is an impacted stone deep in the common duct or in the ampullary region, for removal of stones from this approach may be simpler than from an incision in the common duct.

Once the diagnosis has been made, there seems little reason to doubt the efficacy of resection if it is technically possible. It has been stated by some that the results of sidetracking operations, such as cholecysto- or choledocho-gastrostomy, duodenostomy, or enterostomy, are so satisfactory, with such a low mortality, that they should be used instead of resection in the presence of carcinoma of the head of the pancreas. However, there are a few figures cited for the survival time of those patients who have only sidetracking operations, and in these reports it is rarely stated that the average survival is more than six months; if one carefully observes the figures cited, it is not infrequently to be noted that the mortality of sidetracking operations is, if not as high, almost as high, as that of resection in any one group.[17]

This series, with an operative mortality for palliative surgery of 38% compared with a mortality of 33.3% for resections and an average survival of 5.4 months with palliative treatment as opposed to 2.5 years with resection, would not seem to support this opinion. Similar results are reported by others.

It should be noted that none of the 12 patients who underwent resection had reimplantation of the pancreatic duct. Despite this, only one survivor showed uncontrollable metabolic disturbances. Pancreatic fistula or drainage was a real problem in only one case (Case 2), reported in detail in this paper. Many surgeons have felt that reimplantation of the pancreatic duct is of great importance, and several procedures have been devised to facilitate this additional procedure.[18]

SUMMARY

One hundred thirty-five cases of carcinoma of the pancreas, ampulla of Vater, the ducts within the head of the pancreas, or duodenum have been reviewed, and in 122 the tumor has been found to occur in the region of the head of the pancreas. In 75 of these the diagnoses were pathologically proved, in 21 at autopsy. In 19 of the cases with proved diagnoses the patient had a palliative type operation, with an operative mortality of 57.8% and an average survival of three and one-half months.

Twelve pancreatoduodenectomies were performed for carcinoma in the region of the head of the pancreas, with a mortality of 33.3% and an average survival of over two and one-half years for those who were operated upon more than one year before the preparation of this report. Three patients still survive—one over six years, one over one year three months, and one over six months.

REPORT OF CASES

CASE 1.—G. L. was admitted to the hospital because of jaundice of two and one-half months' duration. On Aug. 2, 1938 he was operated upon by Dr. A. W. Oughterson with a preoperative diagnosis of (1) silent common duct stone, (2) carcinoma of the pancreas, or (3) carcinoma of

17. Child.[3] Dennis.[14]

18. Zinninger, M. M.: Radical Resection of Duodenum and Head of Pancreas for Carcinoma of Ampulla of Vater, Cincinnati J. Med. **23**:174-176, 1942. Varco, R. L.: A Method of Implanting the Pancreatic Duct into the Jejunum in the Whipple Operation for Carcinoma of the Pancreas, Surgery **18**:569-573, 1945. Pearse, H. E.: Should We Standardize the Reconstruction After Pancreaticoduodenectomy? Surgery **20**:663-669, 1946.

the ampulla of Vater. A small papillary carcinoma in the region of the ampulla was removed by a wedge resection, including a segment of common and pancreatic duct and a small portion of the head of the pancreas. He first showed evidence of local recurrence in February, 1945 (five and one-half years), and a cholecystojejunostomy was performed on March 19, 1945, with death resulting on Nov. 9, 1945, six years two months after his first operation.

CASE 2.—H. M., a 44-year-old man, was first seen in the New Haven Hospital outpatient department in March, 1940, when diagnoses of angioneurotic edema, exogenous obesity, and epidermophytosis had been made. He was first admitted to the New Haven Hospital on June 10, 1941. Three months earlier he had noted an indefinite right hypochondriac and epigastric pain, which was also associated with back pain in the midlumbar region. At the onset of this pain

Fig. 1 (Case 2).—Roentgenogram showing deformity of duodenum.

he was nauseated and vomited undigested food for several days, but since then there had been no vomiting. The pain persisted with increasing severity, and approximately six weeks before admission, treatment for a peptic ulcer was started by his local physician. This gave him partial temporary relief, but the symptoms recurred one week after the institution of the diet and 10 days before admission to the hospital they became very severe. Two days before admission the patient first noted jaundice, dark urine, and light stools. He had lost 10 lb. (4.5 kg.) in weight during the three weeks before admission and had noted increasing fatigue and weakness.

The results of routine laboratory studies, including blood count and urinalysis, were essentially negative except for the presence of bile in the urine. The stools were light brown and formed with bile present, and with a negative guaiac reaction on five occasions. The icterus index was 35, rising on June 17 to 65, when he had a positive direct van den Bergh reaction (25 mg. per 100 cc.). A gastric analysis was done on June 12, 1941, and a small quantity of colorless fluid

was obtained without free hydrochloric acid; after the administration of histamine 15 cc. of colorless, cloudy fluid was obtained with 2.8 units of free hydrochloric acid and 4.2 units of total hydrochloric acid. The upper gastrointestinal tract series showed a prepyloric ulcer, questionably malignant, and a duodenal ulcer with a demonstrable crater. In addition, there was displacement of the distal stomach and duodenum, thought to be due to a questionable carcinoma of the head of the pancreas (Fig. 1). The barium enema study gave completely negative results. The upper gastrointestinal tract series was repeated on July 14, with similar findings reported.

An exploratory laparotomy was carried out by Dr. J. Hirschfeld on June 23, and it was noted that the gall bladder was greatly distended, the common duct was dilated to about the size of

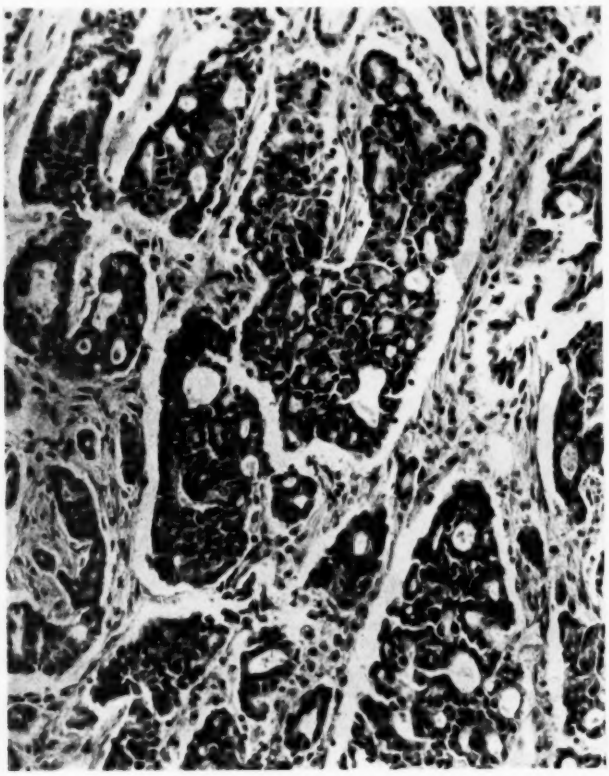

Fig. 2 (Case 2).—Microscopic section from head of pancreas; × 190.

the operator's thumb, and in the region of the head of the pancreas below the first portion of the duodenum a firm mass, which was free and movable, about 3.5 by 4 cm., was palpated. There was also thickening in the pyloric region of the stomach which probably represented an ulcer. It was felt that the tumor was probably resectable and an enteroenterostomy and a Roux-Y type of cholecystojejunostomy were performed.

On July 21, the second stage was carried out by Dr. A. W. Oughterson, at which time it was noted that the tumor had decreased in size since the previous exploration. The gastric portion of the operation was first carried out with a resection of the distal fourth and a gastrojejunostomy was established. The common duct was then isolated and triply ligated. The large vessels were next dissected, the portal vein was identified, and the branches from the pancreas were isolated and ligated. The pancreas was then divided over the portal vein and the superior mesenteric

vessels. The distal, or tail, end of the pancreas was closed with a mattress suture of silk. The remainder of the resection was then carried out in the usual way from medial to lateral, including the head of the pancreas and the duodenum. The stump of the distal duodenum or jejunum was closed with inversion sutures of the Parker-Kerr type reinforced with interrupted silk sutures.

The pathology examination was reported as showing a 2 by 3 cm. tumor mass just adjacent to the duodenum. The remainder of the head of the gland was very firm and resistant and probably contained secondary nodules of tumor. The distal 1 cm. of the common duct was compressed by tumor, with almost complete obliteration. The ampulla of Vater was found, and the pancreatic

Fig. 3 (Case 3).—Gross pathological specimen showing malignant erosion of duodenal mucosa about papilla of Vater, with main mass in head of pancreas; × 190.

duct was traced to the midportion of the head of the gland, at which point it became completely obstructed by tumor. Two lymph nodes were found attached to the outer surface of the pancreas. On cut section they appeared to be normal lymph nodes.

Microscopic Pathology.—Sections through the tumor mass (Fig. 2) showed irregularity of cell outlines and nuclei with a tendency toward formation of acini, and in some areas solid masses of cells were seen in the stroma. A few mitotic figures were seen. No evidence of involvement of the lymph glands was noted. The pathological diagnosis was adenocarcinoma of the pancreas.

Postoperatively atelectasis of the lower and middle lobes of the right lung developed, and the patient had a temperature rise to 101.8 F. on the first day. However, his subsequent course was

not remarkable, except for the development of drainage from the upper end of the wound on the 2d postoperative day; this continued to the 11th postoperative day, when bile was also found to be draining from the same tract. This bile drainage continued for five days and then ceased. At the time of discharge, on the 31st postoperative day, there was still some drainage of pancreatic juice from the wound.

The patient was readmitted in July, 1942, for treatment of hemorrhoids, at which time he was doing very well. He had been working a 10-hour day six days a week as a toolmaker. He was followed regularly in the tumor clinic until August 1945, when he first complained of gas pains

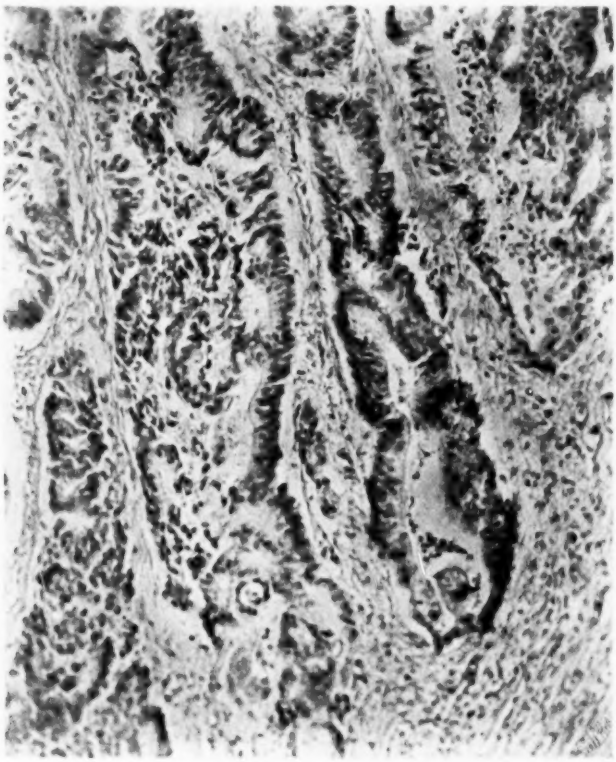

Fig. 4 (Case 3).—Microscopic section from head of pancreas; × 190.

in the midabdomen and a weight loss of 20 lb. (9.1 kg.) in the previous three months. However, he was still rather obese and continued to work. This was four years two months following his operation.

An upper gastrointestinal x-ray series, on Aug. 26, 1945, showed medial anterior displacement of the stomach. The patient continued to lose weight and in October, 1945, he had a period of gastrointestinal bleeding with tarry stools. It was at this time that he ceased working, four years six months following his operation. He returned to work, however, and in November, 1945, after a severe strain bilateral hernias developed. He continued to go downhill slowly thereafter, with continuation of the upper abdominal complaints. He had at least six episodes of hemorrhage of the gastrointestinal tract during this period. A repeat gastrointestinal series was obtained in June, 1946, but there was no evidence of a marginal ulcer.

In July, 1946, abdominal fluid was first discovered and a small mass in the region of Blumer's shelf was first palpated.

The patient needed several paracenteses thereafter, and after the paracenteses he improved in general, with a marked improvement of his appetite. It was felt that some of the ascites and edema of the scrotum and legs was due to low serum proteins and secondary to the hemorrhages.

The patient finally died on Nov. 2, 1946, five years five months following operation.

Case 3.—E. M. J., a 52-year-old white woman, was first admitted to New Haven Hospital on June 13, 1945, with a chief complaint of abdominal pain of two days' duration. She gave a rather bizarre history of general upper abdominal bloating and gas of 20 years' duration and

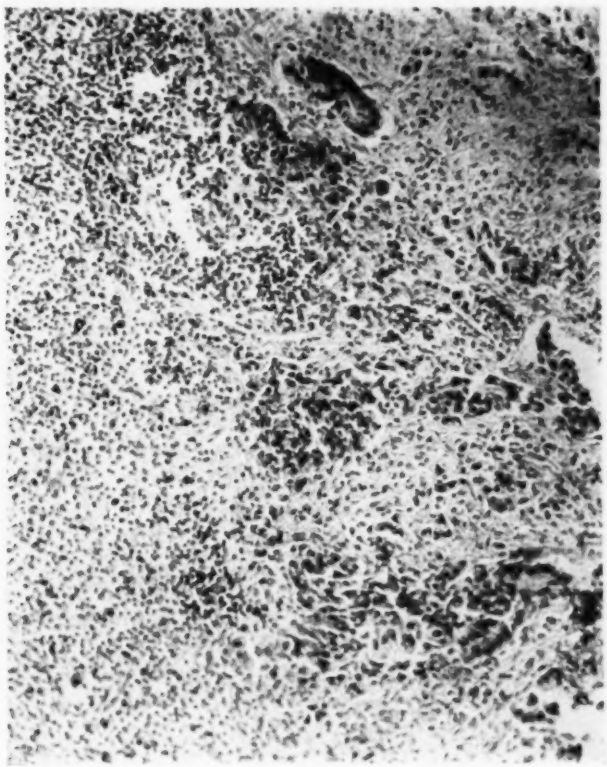

Fig. 5 (Case 3).—Microscopic section from lymph node; × 190. Poor contrast is due to fading of stain, but nests of malignant cells are obvious.

a definite history of sudden onset of abdominal pain, nausea, vomiting, jaundice, and acholic stools two years earlier. At another hospital a cholecystectomy had been performed with a preoperative diagnosis of obstruction of the common duct of undetermined cause and a postoperative diagnosis of obstruction of the common duct, cholecystitis, and choledochitis with hydrops of the gall bladder and the common duct. Incidentally, it was stated that the common duct was explored by palpation with the fingers and by instruments after the common duct was opened, and then a lead probe was passed down into the duodenum after the spasm in the region of the ampulla of Vater was broken through. No stones were located. A T-tube was placed in the common duct. It was also stated that the pancreas showed no gross pathology.

She continued to have attacks of abdominal pain during the two years with several attacks of jaundice, at first precipitated by fatty meals according to the history, but finally with no specific

relationship to food. Four days before admission to New Haven Hospital she took a laxative without effect. This was repeated on the next day, and after this severe, sharp, persistent, cramping, nonradiating epigastric pain developed and steadily increased in severity. The urine became very dark. Icterus and itching of the skin developed. During the two-year period she had lost 40 lb. (18.1 kg.) in weight.

The past history was unremarkable, except for menstrual difficulties which had been controlled by implantation of radium into the uterus.

A physical examination disclosed nothing remarkable, except for the abdomen, in which there was generalized muscle spasm and marked right upper quadrant tenderness. The laboratory

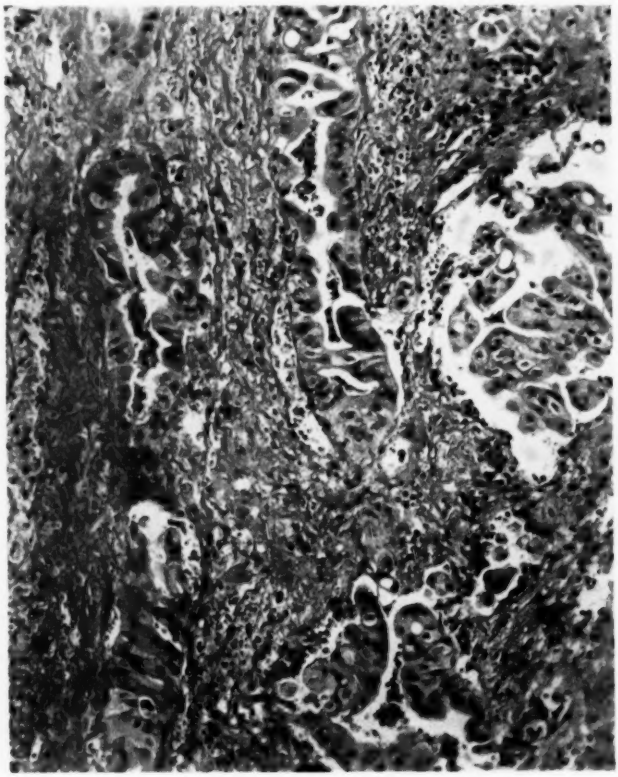

Fig. 6 (Case 4).—Microscopic section from mass in region of stump of common duct removed at operation two years nine months after pancreatectomy; × 190.

work revealed anemia (3,390,000 red blood cells, and 10.5 gm. of hemoglobin) and a white blood cell count of 13,000, with 93% polymorphonuclear leucocytes. The urine was normal except for a few casts and the presence of bile. The impression was recurrent common bile duct obstruction due to stones.

The patient was discharged after the subsidence of the acute attack and was readmitted on June 28, 1945, because of persistent jaundice. At this time she showed essentially the same blood and urinary findings except that she had a normal white blood cell count with a normal differential count. Laboratory reports from her previous admission revealed an icterus index of 15, a serum bilirubin level of 5.8 mg. per 100 cc., a 1+ cephalin flocculation reaction in 48 hours, alkaline phosphatase of 63.75 units, and a serum protein of 7.29 gm. per 100 cc. A van

den Bergh reaction was positive. On July 1, 1945, the fifth day following admission, exploratory laparotomy was performed with a preoperative diagnosis of partial common duct obstruction. On palpation, the head of the pancreas was found to be nodular and densely hard. A radical resection was performed by Dr. S. C. Harvey essentially as in Case 2. No involved lymph nodes were palpated during the procedure. The pathology report, in brief, was as follows: The duodenum was opened, and 2 cm. proximal to the ampulla of Vater the mucosa was ulcerated and an irregular fungating white hard mass was seen; it measured about 5 by 5 by 2 cm. This mass also involved the common duct and the head of the pancreas (Fig. 3). One of the lymph nodes on the surface of the pancreas was involved by direct extension of the tumor. Section

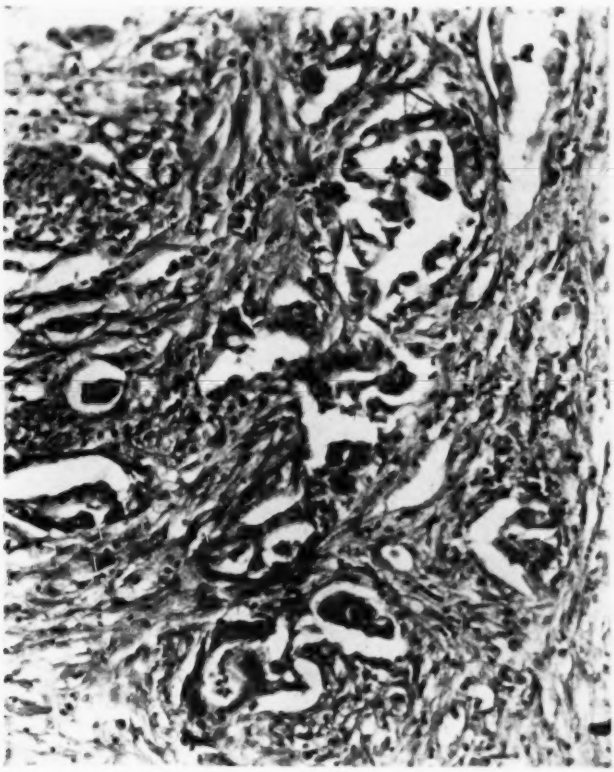

Fig. 7 (Case 4).—Microscopic section from head of pancreas resected May 22, 1945; × 190. This section also suffers from poor contrast as a result of fading.

through the pancreas at the cut end revealed marked fibrosis with nothing but islet cells and ducts remaining, with much round-cell infiltration. Section through the tumor in the pancreas and the wall of the duodenum showed numerous gland-like structures and cords of cells of irregular size and shape and with numerous mitoses (Fig. 4). The involved lymph nodes showed definite carcinomatous areas (Fig. 5).

The patient's postoperative course was uneventful except for the development of a large bowel obstruction on the fifth postoperative day, treated by cecostomy. She was discharged on July 22, the 21st day following operation. She has been followed since that time, with no evidence of recurrence. Her appetite has been fair to good, and her state of nutrition was excellent until March, 1951, when she was losing weight, with diarrhea, and seemed to be going downhill.

However, after the institution of therapy with bile salts and pancreatin, she showed marked improvement and has continued well to her last follow-up report, Sept. 10, 1951, over six years following the resection.

CASE 4.—R. H., a 56-year-old white woman, was admitted to New Haven Hospital on April 23, 1945, with a history of jaundice of one week's duration but with a weight loss of 15 to 20 lb. (6.8 to 9 kg.) over a period of a few months. On physical examination the gall bladder was distended and the liver was enlarged (down 4 fingerbreadths) and firm. The icterus index was 50, and the serum bilirubin level was 12 mg. per 100 cc. X-rays were read as showing extrinsic pressure on the duodenum, hepatomegaly, and questionable hydrops of the gall bladder. The urine contained sugar (4+).

On May 9, 1945, an exploratory laparotomy and a cholecystojejunostomy were performed. On May 22, the head of the pancreas and duodenum were resected and a gastrojejunostomy was made distal to the cholecystojejunostomy. The pancreatic and common ducts were ligated. Both operations were performed by Dr. E. A. Lawrence.

The postoperative course was satisfactory, the only distressing factor being a biliary fistula which developed on the 18th postoperative day. The patient was discharged on the 31st postoperative day, June 23. The fistula closed during a second admission, from July 2 to July 16.

She was readmitted on Nov. 30, 1946, for 14 days with a diagnosis of interstitial pancreatitis, diabetes, and abdominal hernia.

She was again admitted on Nov. 3, 1947, because of a gastrointestinal hemorrhage and was discharged on Dec. 12, 1947. Nine days later Dec. 21, she was again admitted, this time with jaundice, and she was discharged on Jan. 9, 1948. Jaundice continued to increase, and she was admitted for the sixth and final time. Exploration was carried out on Feb. 6, 1948, and a supposedly inflammatory mass was found in the region of the junction of the cystic and the common duct. This mass was removed with the gall bladder and the attached jejunum and a choledochojejunostomy performed. Histological examination revealed carcinoma (Fig. 6), which in retrospect was very similar in appearance to the lesion in the head of the pancreas (Fig. 7) removed two years nine months before.

ACUTE HEMORRHAGIC PANCREATITIS

Report of a Case with Cortisone Treatment

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THIS CASE is presented to suggest a possible beneficial adjunct in the therapy of acute hemorrhagic pancreatitis.

REPORT OF CASE

J. S. (48600-51 Bellevue Hospital), a 25-year-old white woman, was admitted to the Fourth Surgical Division on July 31, 1951. For the past three years she had been troubled with recurrent attacks of right upper quadrant pain; the last attack occurred one month prior to admission, shortly before a Caesarean section was performed. Her postpartum course was uneventful. Five days before admission she noted the onset of a similar episode associated with nausea, vomiting, and pain radiating to her back. She was seen twice during this interval in the outpatient clinic, where she was given medication and sent home.

On admission the patient appeared acutely ill. The temperature was 103.8 F. The blood pressure was 120/70, and the pulse was 128. She was perspiring profusely and appeared to be bordering on a state of shock. The heart and lungs showed no abnormalities. The previous laparotomy incision was well healed. There was tenderness and spasm in the right upper quadrant and epigastrium. Pelvic examination revealed a subinvoluted uterus, which was tender on movement. The leucocyte count on admission was 18,200; the hemoglobin was 70%, and the hematocrit reading was 35%. An emergency scout film of the abdomen was negative. A tentative diagnosis of acute cholecystitis was made.

The following therapy was begun: A Levin tube attached to a Wangensteen suction apparatus was inserted into the stomach. Antibiotic therapy consisted of penicillin, 400,000 units intramuscularly twice a day, dihydrostreptomycin, 0.5 gm. intramuscularly twice a day, and aureomycin, 500 mg. intravenously. Despite attempts to actively hydrate the patient, the temperature continued to rise. At midnight on the day of admission it was 106 F., in spite of alcohol sponges and ice-water enemas. The following morning the patient's condition became worse; the respiratory rate became rapid, and the pulse weak and irregular. She was placed in Trendelenburg position and a blood transfusion of 500 cc. was begun. Despite the addition of 0.1% phenylephrine hydrochloride (neo-synephrine®) intravenously, intravenous administration of 3 liters of dextrose, transfusion of 1,000 cc. of blood, and nasal administration of oxygen, the patient remained in profound shock. Throughout the day the systolic blood pressure remained between 50 and 60 mm. Hg. Respirations continued at about 45 per minute. The patient was placed on "critical" service. By evening no blood pressure was obtainable. It was felt the patient was rapidly nearing death.

At 8 p. m. on Aug. 1, 1951, neither a blood pressure reading nor a pulse was obtainable, nor could respirations be easily observed. Hence cortisone acetate, 100 mg., was admin-

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The cortisone used was supplied by Merck & Company, Inc., Rahway, N. J.

From the Department of Surgery, New York University Post-Graduate Medical School, and the Fourth Surgical Division (New York University) of Bellevue Hospital.

istered intramuscularly. The patient received her second dose of 100 mg. of cortisone on Aug. 2, 1951, at 2 a. m. At 4 a. m. a very faint pulse was felt, and a blood pressure of 94/84 was obtained. On Aug. 3, 1951 at 8 a. m., the patient appeared improved and was given her third dose of 100 mg. of cortisone. She appeared more alert, but examination of the abdomen revealed signs of a generalized peritonitis. She was seen by several attending surgeons, who agreed that a ruptured gall bladder might be present and that immediate laparotomy was indicated. Accordingly the patient was taken to the operating room, where the abdomen was entered through a small right upper quadrant subcostal incision under local procaine block. When the peritoneum was opened, the diagnosis became evident at once. A large amount of thin, blood-tinged fluid was present, and there were multiple areas of whitish calcified-appearing plaques scattered over the omentum. A biopsy of one of these was taken. The gall bladder was normal in appearance with no palpable stones. The abdomen was closed without drainage. Pathological examination confirmed the diagnosis of fat necrosis.

Blood for serum amylase had been drawn on admission and on the morning of the operation. Through a misunderstanding a determination was done only on the second specimen and was reported postoperatively as 6.05 mg. per cubic centimeter (Myers-Free-Rosinski method—normal 1 to 2.5 mg. per cubic centimeter).

Her subsequent course was marked by a pronounced renal shutdown for two days, there being a urinary output of 155 cc. the first 24 hours and 350 cc. the second 24 hours. The blood urea nitrogen was 100 mg. per 100 cc. on Aug. 7, 1951. She became euphoric and wanted to sign herself out of the hospital. This condition persisted for two days. Her temperature ranged between 102.2 and 101 F. from Aug. 5 to Aug. 12, 1951. During the following week it ranged between 101 and 99 F. The patient improved progressively, and she was discharged in good condition on Aug. 21, 1951, at which time the blood urea nitrogen was 17.4 mg. per 100 cc., and the serum amylase was 1.5 mg. per cubic centimeter.

At present, seven months later, she is doing well.

COMMENT

This case of acute hemorrhagic pancreatitis is the first, to our knowledge, to have been treated with cortisone. Because of the apparent response to cortisone at a point when the patient appeared almost certainly dying, presentation of this case appears warranted.

The patient's response to cortisone was somewhat similar to the experience of Nelson and Goldstein [1] and Newman,[2] who used cortisone in treating the Waterhouse-Friderichsen syndrome. An appreciable change in the condition of their patients was noted within four to six hours after administration of cortisone. In our patient the blood pressure was obtainable for the first time eight hours after her original dose of 100 mg. of cortisone.

Further investigation of a possible role of cortisone in the treatment of acute hemorrhagic pancreatitis has been under way in our animal laboratory for several months.

SUMMARY

The case history of a patient with acute hemorrhagic pancreatitis is presented. Included in our therapy was the use of cortisone at a point in her disease when severe shock was present and death appeared imminent. The recovery of the patient appears to have been influenced favorably by the cortisone.

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2. Newman, L. R.: Waterhouse-Friderichsen Syndrome: Report of Cure Effected with Cortisone, J. A. M. A. **146**:1229 (July 28) 1951.

ADRENAL HORMONES AND INCREASED CAPILLARY PERMEABILITY OF BURNS

An Experimental Evaluation

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AND
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IN RECENT medical journals and pharmaceutical literature the statement has been made that corticotropin (ACTH) has a beneficial effect upon capillary permeability, diminishing the losses of water and protein from the circulation of burned patients, and thus reducing their plasma and electrolyte requirements.[1] If confirmed, such claims would mean a significant advance in the therapy of burn shock, especially in the event of any mass disaster. The consequence, if treatment were based on these claims and they proved incorrect, would be a rising tide of unnecessary deaths from hemoconcentration and dehydration in extensively burned patients. In view of this possible consequence we are reporting studies concerning the action of pituitary and adrenal hormones on the permeability of the vascular membrane.

The loss of fluid occasioned by a burn wound is caused both by heat and by infection. The heat damages capillaries; it increases their permeability, and fluid pours into the wound, collecting as edema and seeping out onto the wound surface. As the capillaries heal, leakage diminishes, resorption of the edema fluid gains pace, and the edema subsides.

Infection, a common sequel of a burn wound, may also be accompanied by fluid loss due to the increased capillary permeability of infectious inflammation. Although infection may complicate the burn wound at any time, infectious inflammation requires time to develop and is, therefore, not present to a significant degree in the initial hours after burning. In order to limit the variables, our study has centered on capillary damage in the initial hours after injury. The phase of edema resorption will be dealt with in a subsequent publication.

The work described in this paper was done under contract between the Office of Naval Research and Harvard University.

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EXPERIMENTAL PROCEDURES

The cannulated lymphatic preparation in the dog, introduced by Drinker and his co-workers,[2] was selected for the study. This preparation gives reproducible, objective evidence of capillary permeability. Both lymph flow and lymph protein concentration are readily measured, and their changes reflect alterations of capillary permeability and tissue fluid pressures. With increased capillary permeability there is an outpouring of plasma fluid and protein into the tissue spaces, resulting in a rise in flow and protein concentration of the lymph.

Spontaneous anatomic variations in the size and number of lymphatics and the position of the valves within them affect the magnitude of lymph flow in any one lymphatic vessel. The effects of these variations can be minimized by ligation of specified areas of lymphatic collaterals, use of the largest possible cannulae, and perforation of the valves, but they cannot be completely eliminated. Therefore, in interpreting the lymph-flow curves, more attention is to be paid to the time of onset of increased flow and the time at which peak flow is reached than to the maximum height of flow attained. No technically poor preparations have been included in the experiments reported. The lymph protein concentration is not appreciably altered by these anatomic variations in the lymphatics.

Mongrel dogs of both sexes were used. They varied in weight from 12 to 24 kg. Intraperitoneal pentobarbital sodium anesthesia was used. Lymphatic trunks in one or both hindlegs were cannulated above the ankle. The lymph was heparinized, collected, and weighed to determine the flow per minute. Its protein content was measured by refractometer, with checks from time to time by the Kjeldahl method. The serum protein was determined by the Kjeldahl method, and hematocrit levels were measured on heparinized blood in 2-cc. tubes of 5 mm. diameter.

Burns were produced by immersing the dogs' feet in water at 90 C. for 10 seconds. This temperature and duration of exposure was chosen because of previous experience with the cannulated lymphatic preparation in burned animals.[3] In dogs weighing less than 20 kg. the depth of immersion was 10 cm.; for larger animals it was 12 cm.

Large doses of the anterior pituitary or adrenal hormone were given to assure effective concentration. In a number of the experiments they were administered prior to infliction of the burns. Although pretreating the animals in this manner can obviously have no clinical parallel, it was important to do so experimentally to be sure the corticotropin and cortisone were physiologically effective during the period when capillary permeability was under study.

In the experiments using corticotropin, 2 to 6 mg. per kilogram of body weight were injected intramuscularly at varying intervals before and/or after the burns. Supplementary injections of 1 to 6 mg. per kilogram were also given intravenously in a few instances. In the experiments using cortisone, the majority of the dogs received 100 mg. of cortisone acetate intramuscularly on the day prior to burning and subsequent doses of equal strength on the morning of the burn, one dose being given to most of the animals just four hours prior to the immersion in the hot water. Only one dog in the cortisone series received no hormone until after the first leg had been burned. This dog was then given two doses of 100 mg. each three hours apart.

As a check on the pharmacological efficacy of the hormones and the dosage used, eosinophile counts were done before, during, and at the end of each experiment. The phloxine-propylene-glycol method of Randolph[4] was used, free-flowing drops from venopuncture needles being taken up directly into the counting pipettes and diluted as rapidly as possible. Dog eosinophiles stain poorly and in some animals they do not appear at all pink. Careful adjustment of the microscope substage condenser, however, will make them appear darker than other noneosinophilic white cells, so that reproducible counts can be obtained.

2. Field, M. E.; Drinker, C. K., and White, J. C.: Lymph Pressures in Sterile Inflammation, J. Exper. Med. **56**:363, 1932. Glenn, W. L.; Peterson, D. K., and Drinker, C. K.: Flow of Lymph from Burned Tissue with Particular Reference to Effects of Fibrin Formation upon Lymph Drainage and Composition, Surgery **12**:685, 1942.

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4. Randolph, T. G.: Blood Studies in Allergy: I. The Direct Counting Chamber Determination of Eosinophils by Propylene Glycol Aqueous Stains, J. Allergy **15**:89, 1944.

The volume of edema developing in the burned feet was measured by fluid displacement in a plethysmograph. In all cases the foot being measured was immersed to a mark 2 cm. below the upper limit of the burn. In one case additional volume measurements were made with the foot immersed to 2 cm. above the burn. The accuracy of the plethysmographic method employed was not better than plus or minus 10 cc.

RESULTS

Lymphatic cannulation was carried out on 24 dogs. Eight received no therapy and constituted controls. The findings in this control group were consistent with those previously obtained in untreated animals in this laboratory.[3] Seven dogs were treated with cortisone and nine with corticotropin.

Controls.—In all control dogs the concentration of protein in the lymph recovered prior to burning was in the vicinity of 1 gm. per 100 cc. Following the burn a

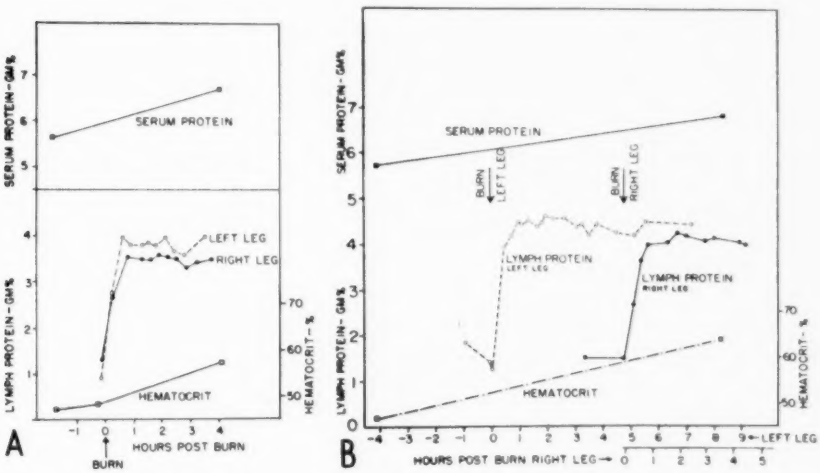

Chart 1.—Pattern of rise in protein concentration of lymph and serum in untreated burned dog. Hindlegs only were burned. The burns in this and all subsequent experiments were at 90 C. for 10 seconds. *A* (Dog 15-51), effect of simultaneous burn of both legs. The rises encountered, including that of the hematocrit, are typical for a burn of this intensity. *B* (Dog 24-51), effect of an initial burn on pattern of a subsequent burn. A four and one-half hour delay in burning the second leg failed to influence significantly the rises in protein concentration. The eosinophile counts for this dog were 1,181 prior to cannulation, 584 three hours after the first leg was burned, and 22 three and one-half hours after the burning of the second leg.

prompt, steady rise occurred till a stable level was reached between 3.5 and 5.4 gm. per 100 cc. The peak was reached after the first and before the second hour (Chart 1*A* and *B*).

Lymph flow from the feet is minimal in pentobarbital-anesthetized, unburned dogs. In order to obtain the lymph needed for analysis, it was occasionally necessary to massage the paws gently. Following a 90C. burn, there is a prompt, spontaneous flow, reaching a peak in from one to three hours. Peak values in the control dogs ranged from 58 to 360 mg. per minute. A typical curve is seen in Chart 2. Following the rise there is a somewhat more leisurely fall. This fall can be transiently interrupted, and a brief rise in flow can be produced by trauma to the contralateral leg.

In the charts the curves of the foot volume accompany those of the lymph flow. All the plethysmographic measurements on control dogs showed a gradual increase in swelling, reaching a constant level in from one to three hours after burning. As in the previous studies using this technique,[5] lymph flow began to decline close to the time maximum local edema was reached. Presumably, the rising tissue pressure offsets the capillary filtration pressure.

In the single experiment in which the foot volumes were measured both below and above the level of the burn, the peak was noted earlier in the burned area.

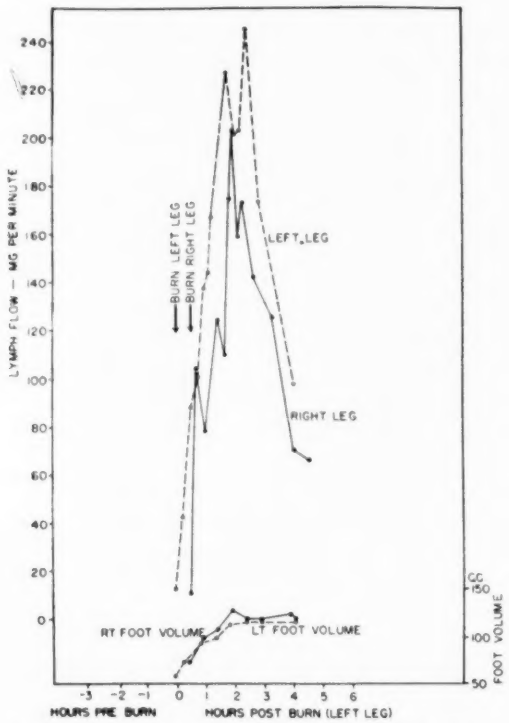

Chart 2 (Dog 14-51).—Patterns of rise and fall in lymph flow and increase in foot volume in untreated burned dogs. Typically a prompt rise in lymph flow occurred after burning. A peak was reached in from one to three hours, and flow diminished thereafter. The foot volumes, as measured by immersion of the legs to 2 cm. below the upper limit of the burn in a plethysmograph, also reached a maximum in from one to three hours. The eosinophile counts on this control dog were 500 per cu. mm. prior to cannulation, 588 per cu. mm. before burning and after cannulation, and 131 per cu. mm. three and one-half hours after burning. In untreated dogs the eosinophile count may rise or fall after cannulation, but always falls after burning.

This suggests seepage of edema upward into the unburned tissues after local edema reaches its peak. The watery appearance of the unburned tissues of the legs, when they were incised after the animals were killed, supported the clinical impression of extension of edema fluid above the burn limits.

5. Rhinelander, F. W.; Langohr, J. L., and Cope, O.: Explorations into the Physiologic Basis for the Therapeutic Use of Restrictive Bandages in Thermal Trauma, Arch. Surg. **59**:1056, 1949.

Serum protein values rose in all control dogs, the average initial and final levels being 5.9 and 6.5, a rise of 0.6 gm. per 100 cc. This rise in serum protein concentration is typical of the serum protein change occurring in the untreated burned animal.[6] The hematocrit values rose similarly from an average value of 50.3% to 62.8%. (The data of hematocrit levels, serum protein concentrations, eosinophile counts, and foot volumes are given in the accompanying table.)

Eosinophile counts in this group of control dogs showed a tendency to fall during cannulation, with an average drop of 30%. In two cases, however, a very slight rise was seen during cannulation. In all animals the eosinophile counts fell following the burns. Final counts averaged 17% of the initial levels.

Corticotropin-Treated Dogs.—The observations relating to capillary permeability in the corticotropin-treated dogs did not differ significantly from those in the controls. Initial and final values for lymph protein concentration were the same in corticotropin-treated dogs as in the controls, whether the hormone was administered before or after the burn trauma. The curves in the two groups, controls and treated dogs are practically superimposable (Chart 3, *A* and *B*).

Lymph flow in the unburned state was minimal in these dogs, and following burning it increased in all animals, reaching a peak in one to three hours regardless of the time at which corticotropin was administered (Chart 4). Peak values ranged from 87 to 849 mg. per minute. The rate of fall was the same in the corticotropin-treated animals as in the controls. As in the controls, burn trauma to one leg produced a slight increase in flow in the contralateral leg in addition to the effect on the flow in the traumatized limb.

Plethysmographic measurements on corticotropin-treated dogs exhibited the same rate of edema formation with the same leveling off at a peak value after one to three hours seen in the control animals. The average increase in foot volume was 71%, as opposed to 79% for the control animals. The difference has been examined statistically and is not significant.

As in the controls, the hematocrit and serum protein levels rose in all corticotropin-treated dogs, whether pretreated or given the drug only after burning. The average hematocrit reading before the burn was 47.5%, and after the burn 62.3%. The average serum protein level before the burn was 6.3 gm. per 100 cc., and it rose to 6.9 gm. per 100 cc. following the burn.

In the corticotropin group eosinophile counts fell an average of 50% prior to burning. A secondary fall to 15% of the initial level occurred following the burn.

Cortisone-Treated Dogs.—As was the case with corticotropin, the experimental observations in the cortisone-treated dogs did not differ significantly from those in the controls. The curves for the lymph protein values of the cortisone-treated dogs are practically superimposable on the protein curves of the controls (Chart 5). Lymph flow curves proved to have the same shape as in the other two groups, peak values of from 80 to 340 mg. per minute being reached between one-half and three and one-half hours after the burn (Chart 6). The average foot volume increase was 91% above the initial level. Statistical analysis shows that, considering the

6. Cope, O.; Graham, J. B.; Moore, F. D., and Ball, M. R.: The Nature of the Shift of Plasma Protein to the Extravascular Space Following Thermal Trauma, Ann. Surg. **128**:1041, 1948.

Data on Hematocrit Levels, Serum Protein Levels, Eosinophile Counts, and Foot Volumes in Dogs Before and After Burns

	Hematocrit Levels						Serum Protein Levels						Eosinophile Counts									
	Before Burn		After Burn		After-Burn Minus Before-Burn Level		Before Burn		After Burn		After-Burn Minus Before-Burn Level		Before Cannulation		Before Burn		After Burn		Per Cent Drop Before Burn		Per Cent Drop From Initial Level After Burn		Foot Volumes, Per Cent Increase	
	Average, %	Range, %	Average, %	Range, %	Average, %	Range, %	Average, Gm./100 Cc.	Range, Gm./100 Cc.	Average, Gm./100 Cc.	Range, Gm./100 Cc.	Average, Gm./100 Cc.	Range, Gm./100 Cc.	Average	Range	Average	Range	Average	Range	Average, %	Range, %	Average, %	Range, %	Average	Range
Untreated burns	50.3	45.6 to 56.5	62.8	55.4 to 68.5	12.5	6.2 to 17.7	5.9	4.74 to 6.57	6.5	5.47 to 7.00	0.6	0.02 to 1.00	808	169 to 1,369	565	59 to 1,390	152	0 to 494	30	−18 to −65	83	64 to 100	79	56 to 113
Number of animals (8)	(8)		(8)				(8)		(8)				(8)		(6)		(8)						(9)	
Corticotropin-treated	47.5	41.5 to 53.7	62.3	53.5 to 72.0	14.8	5.0 to 22.3	6.3	5.53 to 6.63	6.9	5.82 to 7.55	0.6	0.63 to 1.16	1,203	1,023 to 1,591	655	262 to 1,150	188	53 to 334	50	28 to 74	85	71 to 95	71	41 to 102
Number of animals (9)	(5)		(5)				(5)		(5)				(4)		(3)		(4)						(3)	
Cortisone-treated	45.6	40.9 to 52.3	58.3	50.0 to 64.0	12.7	5.2 to 19.3	6.5	5.3 to 8.7	6.8	5.9 to 7.5	0.3	1.20 to 1.50	1,101	222 to 2,954	360	0 to 906	56	0 to 206	82	64 to 100	98	91 to 100	91	36 to 167
Number of animals (7)	(5)		(5)				(8)		(8)				(5)		(4)		(5)						(6)	

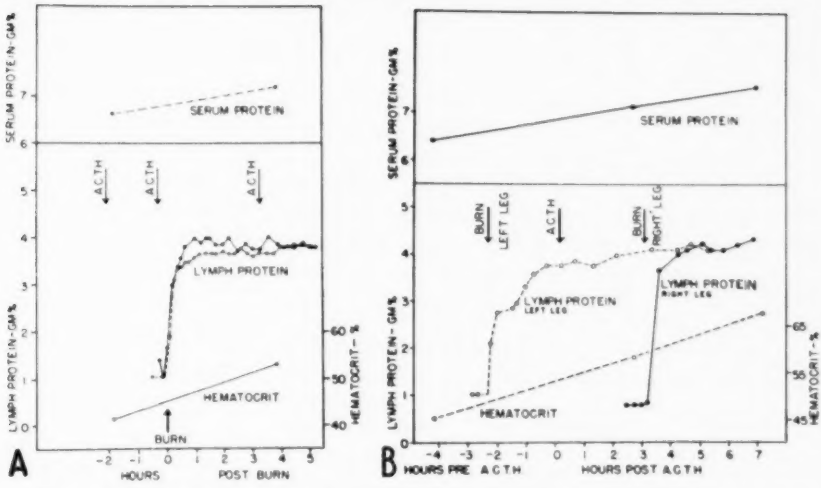

Chart 3.—Pattern of rise in protein concentration of lymph and serum in dogs treated with corticotropin. *A* (Dog 21-51), lack of effect of corticotropin on rise in protein concentrations; 50 mg. of corticotropin was given intravenously and 50 mg. intramuscularly two hours prior to the burn. This dosage was repeated one-half hour before and three hours after burning (total 300 mg.). No significant effects on lymph or serum protein concentrations or on the hematocrit level were noted. The eosinophile count on this dog before cannulation was 1,591. After cannulation and before burning it was 1,150, and four hours after burn it had dropped to 297. *B* (Dog 22-51), lack of effect of corticotropin on rise in protein concentrations when administered after burning the first leg and before burning the second. Corticotropin was given intravenously and intramuscularly (100 mg. each) two and one-half hours after the initial leg was burned and three and one-half hours before the second was burned. The changes in protein concentration of the lymph from the second, or treated, leg are similar to those from the first, or control, leg. The eosinophile count prior to cannulation was 1,153, dropping to 334 at the time of the second burn. Prolonging the interval between corticotropin and the burn in other experiments did not change the pattern of the lymph flow curves appreciably.

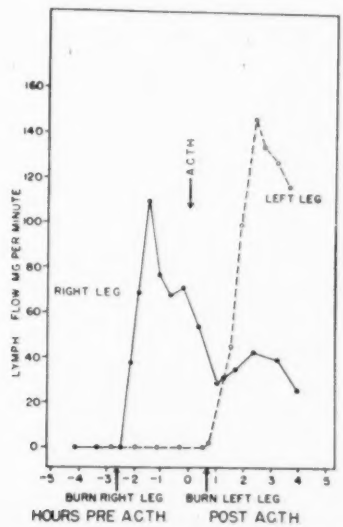

Chart 4 (Dog 2-51).—Pattern of rise and fall in lymph flow in corticotropin-treated dog; 100 mg. of corticotropin was given intramuscularly and 50 intravenously after peak lymph flow from the first burned leg had been reached and 40 minutes before the second leg was burned. Lymph flow from the leg burned after corticotropin increased at essentially the same rate as from the untreated leg. Peak values were reached after similar time intervals. Variations in peak height were also seen in untreated animals and are attributable in large part to anatomic variations in the lymphatics of the two legs.

Prolonging the interval between corticotropin injection and burn did not change the pattern of the lymph flow curves appreciably.

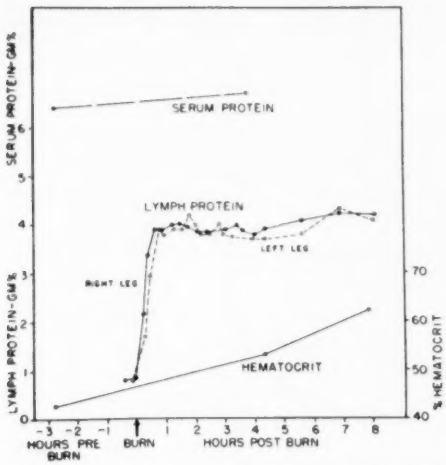

Chart 5. (Dog 8-51).—Pattern of rise and fall in protein concentration of serum and lymph in cortisone-treated dog; 100 mg. of cortisone was administered 25 hours and again at 4 hours before burning. The rises in hematocrit, serum protein, and lymph protein concentration after burning were essentially the same as those seen in untreated animals (Compare Chart 1*A*.).

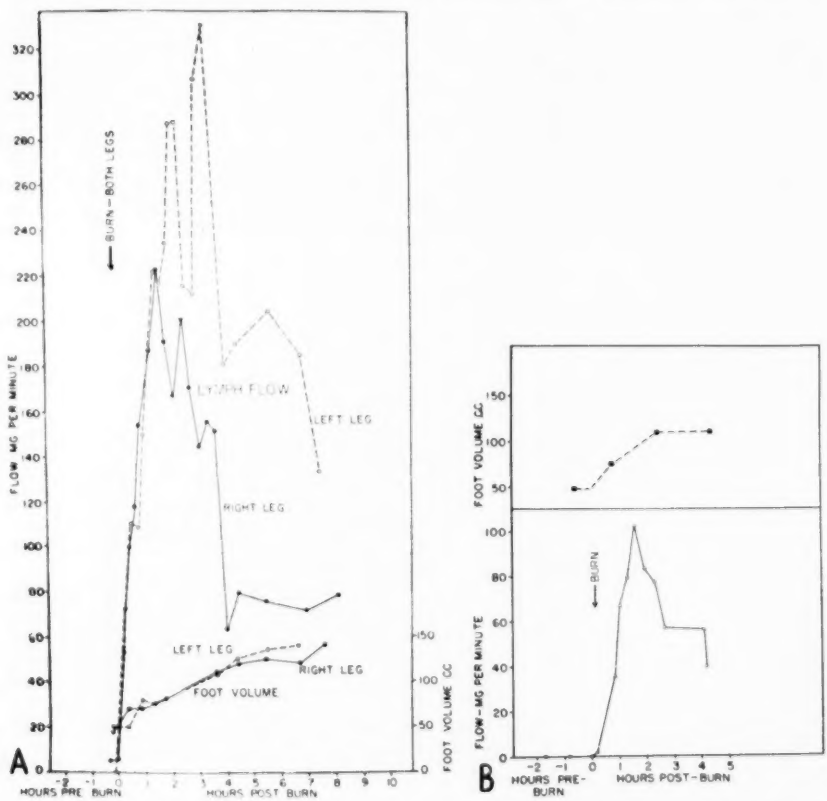

Chart 6.—Pattern of rise and fall in lymph flow in cortisone-treated dog. *A* (Dog 8-51), lack of effect of cortisone administration on lymph flow; 100 mg. of cortisone was given intramuscularly 24 hours before and again 4 hours before burning. Lymph flow and edema of the feet increased as in the control dogs. The eosinophile count showed a 69% drop prior to the second dose of cortisone and dropped after burning to 9% of the initial level. Peak flows of equal magnitude were occasionally seen in control animals. *B* (Dog 6-51), further evidence of lack of effect of cortisone administration on lymph flow; 100 mg. of cortisone was injected intramuscularly 20 hours and again 1¾ hours before burning. The pattern of lymph flow was essentially the same as that seen in control experiments.

sensitivity of the plethysmographic method, this increase is not significantly greater than that for the control or corticotropin-treated animals.

Hematocrit values in the cortisone-treated dogs rose from an initial average of 45.6% to 58.3% after burning, a concomitant rise occurring in the serum protein levels. (Preburn average: 6.5 gm. per 100 cc. Postburn average: 6.8 gm. per 100 cc.) The changes in hematocrit and serum protein levels vary slightly between treated and untreated dogs, but the differences are not significant.

Eosinophile counts on this group of dogs showed an average drop of 82% after administration of cortisone and before burning. The difference between the percentage drops in control and in corticotropin-pretreated dogs before burning could be due to chance alone, whereas the difference between the drops in control and in cortisone-pretreated dogs is significant statistically.

SUMMARY

Twenty-four dogs have been subjected to cannulation of the hindleg lymphatics and burning of the cannulated extremities at 90C. for 10 seconds. Seven dogs were treated with cortisone and nine with corticotropin, the remainder serving as controls. No consistent effect of the hormones was demonstrated on the rate of edema formation, the lymph flow, the lymph protein concentration, the serum protein concentration, or the hematocrit level.

CONCLUSION

Using the Drinker cannulated lymphatic preparation in the pentobarbital-anesthetized dog, we have found no evidence that the abnormal capillary permeability engendered by a burn is influenced by either corticotropin or cortisone. These experiments negate the claims recently made that these hormones are plasma and fluid sparers in the burned patient.

The hormones used in these studies were generously supplied, the ACTH by the Armour Laboratories, and the cortisone by Merck & Co.

Miss Halina Filipak, Mr. Ray Irwin, Mrs. Evelyn Mazzanovich, and Miss Ruth Moore gave technical assistance.

BILATERAL POLYCYSTIC KIDNEY DISEASE

Review of Ninety-Four Cases

CHARLES C. HIGGINS, M.D.
CLEVELAND

BILATERAL congenital polycystic kidney disease has been justly called "the most important malformation of the urinary tract." A review of the literature of the last 20 years, however, reveals that approximately 75% of the cases are not detected or recognized clinically, and an accurate diagnosis is not established until postmortem examination.

The following series of 94 cases have been observed in the Cleveland Clinic from January, 1935, to January, 1951. The diagnoses have been based on detailed histories in which particular attention has been focused on family histories, complete physical examinations, laboratory data, and roentgenologic visualization of the urinary tracts. The latter were secured by intravenous urography, retrograde pyelography, or a combination of the two procedures. Additional diagnostic evidence has been added in some instances either upon surgical exploration or at the time of autopsy examination.

Most of the cases have been followed by recheck urologic survey or by correspondence with the referring physician.

Polycystic kidney disease is a massive involvement of the renal parenchyma by cysts varying in number and size. The condition is congenital in nature, is probably always bilateral, and pursues a slow but progressive course. It follows Mendel's laws of inheritance and may be transmitted equally by either the masculine or the feminine sex.[1] The congenital factors instrumental in the production of polycystic kidney have not been definitely established. Numerous theories have been suggested to explain this phenomena.

The reports in the literature are rather unanimous in accepting this disease as of congenital origin. Cumming[2] presented a family in which the disease was observed in three generations. He cited a family occurrence in 35% of 31 cases. Davis[3] reported an incidence of 14% in his series. In 34 of our 94 cases (37%), we observed that other members of the family had the disease. In recent years it has been our policy to advise members of the immediate family to have a complete roentgenologic investigation of the urinary tract.

In 10 cases (12%) the family history was strongly suggestive as evidenced by deaths between the ages of 45 and 55 from so-called Bright's disease, hypertension, and uremia. Most revealing, all these patients were known to have pronounced enlargement of the kidneys either prior to death or on postmortem examination.

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

1. Hausman, H.: Polycystic Kidney Disease, Am. J. Surg. **49**:335-341 (Aug.) 1940.

2. Cumming, R. E.: Polycystic Kidney Disease, J. Urol. **19**:149-179 (Feb.) 1928.

3. Davis, J. E.: Surgical Pathology of Malformations in Kidneys and Ureters, J. Urol. **20**:283-331 (Sept.) 1928.

Unfortunately, we have been unable to confirm these data through reliable medical sources.

In three instances the family history was not recorded (consultations). In 32 instances (38%) there was no history of renal disease in the family, but in an additional 8 instances family histories of hypertension were elicited. Recently, the father of one of our patients with polycystic kidneys was examined because of profuse hematuria of 24 hours' duration. The intravenous urograms disclosed typical, far-advanced bilateral polycystic renal disease; revealing was the fact that his daughter had stated there was no family history of renal disease. This observation emphasizes the necessity for x-ray studies of all members of the family, not only for the purpose of securing accurate statistical data but also for prompt institution of prophylactic measures for those found affected.

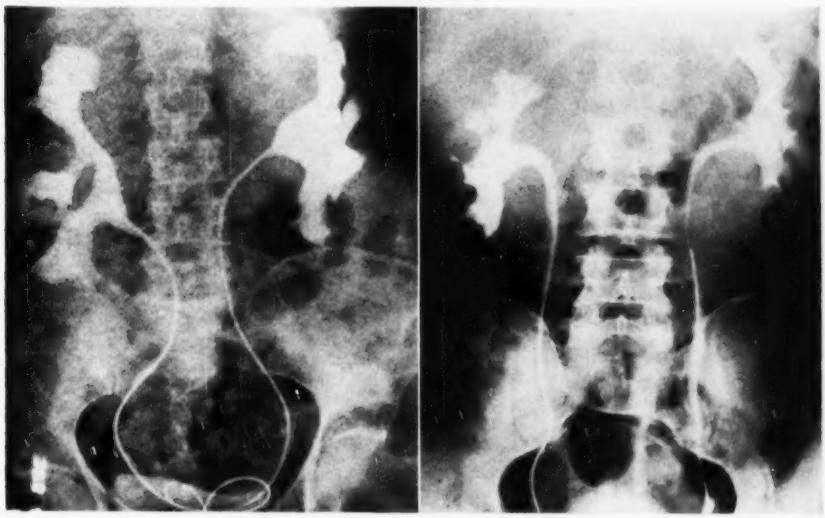

Fig. 1.—Retrograde pyelograms (polycystic kidney).

The condition is, for all practical purposes, always bilateral, which is of aid in differential diagnosis. The case reports presented in the literature as instances of unilateral polycystic disease should not be accepted unless the opposite kidney has been subjected to histologic study. Even in these circumstances the lesion must not be confused with other cystic diseases of the kidney.

Lowsley [4] states: "Simple cysts of the kidney are usually unilateral and single. Not infrequently, however, several do occur simultaneously in the same kidney. These are probably the so-called cases of 'unilateral polycystic disease.'"

Braasch [5] mentioned a case in which the autopsy revealed gross multiple cystic areas in one kidney, while the opposite kidney appeared normal except for fetal lobulations.

4. Lowsley, O. S., and Curtis, M. S.: Surgical Aspects of Cystic Disease of the Kidney, J. A. M. A. **127**:1112-1119 (April 28) 1945.

5. Braasch, W. F., and Schacht, F. W.: Pathological and Clinical Data Concerning Polycystic Kidney, Surg., Gynec. & Obst. **57**:467-475 (Oct.) 1933.

Predominantly unilateral enlargement of the kidney is frequently observed. All our patients were noted to have bilateral involvement, although in many the involvement was predominately unilateral.

The origin of the disease is debatable and obscure. Numerous theories have been proposed. Virchow's [6] theory, accepted for a long time, attributed a papillitis as the causative factor. This was later proved untenable when experimental observations demonstrated conclusively that destruction of renal papillae was followed by atrophy and not cystic degeneration of the excretory tubules.

Many observers believe that the condition was due to a failure of union between the collecting tubules arising from the ureteric bud and the secretory tubules of the nephrogenic blastema. Hildebrandt [7] was of the opinion that the cysts were due to defective union of the ureteral and the metanephrogenic elements.

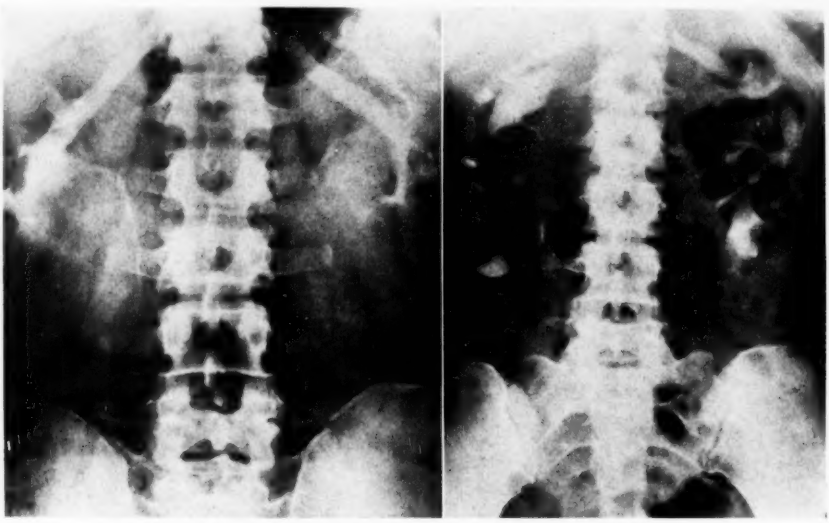

Fig. 2.—Intravenous urograms (polycystic kidney).

McKenna and Kampmeier,[8] in the study of human fetuses and embryos, propounded that, contrary to the theory generally accepted, there are as many generations of secretory as of collecting tubules. The first generation of tubules are vestigial from the onset and are malformed, and many do not have glomeruli. These disappear rather quickly. The following generation of tubules are more developed and usually unite with the collecting ducts. Soon this connection is severed, and the secretory tubules after some cystic dilatation degenerate and then disappear. Later generations of uriniferous tubules form the "growth zone," or definite kidney. When the previous generations of tubules fail to regress entirely, the dilated structures remain to form cysts.

6. Virchow, R.: Virchows Arch. path. Anat. **46**:506, 1869.

7. Hildebrandt, cited by Lowsley, O. S., and Kirwin, T. J.: Clinical Urology, Baltimore, Williams & Wilkins Company, Vol. 2, 1940.

8. McKenna, C. M., and Kampmeier, O. F.: Consideration of Development of Polycystic Kidney, J. Urol. **32**:37-43 (July) 1934.

In 1938, Norris and Herman [9] cited a case of congenital polycystic kidneys in a newborn infant. They stated:

> The kidneys could be divided into three zones. In the papillae, atypical collecting ducts communicated with the calices but not with the cysts. The middle zone was composed of dilated branched tubules among which were numerous anastomoses. In the subcapsular zone were numerous normal mature glomeruli with short uriniferous tubules which were not dilated and ended blindly.

They further stated:

> It is suggested that up to a certain period in fetal life development of the kidneys was normal. Degeneration and cystic changes resulted in dissociation of the nephrons into segments. The continued proliferation of these segments and the retention of secretory products caused the cyst-like dilatation of the tubules and the enlargement of the kidneys. The ultimate course of congenital polycystic kidneys will be found in the germ plasm.

C. R. O'Crowley and H. S. Martland [10] report that most investigators agree that kidney cysts arise from a failure of proper fusion of the secretory and excretory systems (collecting tubules) during the embryonic formation of the kidney, a lack of union between the derivatives of the mesodermal nephrogenic cord and the

Clinical and Autopsy Incidence of Polycystic Kidney Disease

	Clinical	Autopsy
Mount Sinai Hospital, New York	1:3,606	1: 428
Mayo Clinic	1:3,524	1:1,019
Jewish Hospital, Brooklyn (Oppenheimer, 1934)	.....	1: 158
Nauman (cited by Dunger, 1904)	.....	1: 650
London Hospital, London, England (Cairns)	1:4,800	.....
University of Minnesota (Bell, 1935)	.....	1: 509
Cleveland Clinic	1:4,000	.....
Brady Foundation, New York (Lowsley and Kirwin)	34 cases in 19 years	

ureteric buds. They cited three cases of congenital aneurysm of the cerebral vessels associated with large bilateral polycystic kidneys and stated that this illustrates the well-recognized fact that congenital lesions, often of widely varying character frequently may be found to occur simultaneously.

One of the most striking features of polycystic kidneys is their large size. The organs may at times assume enormous proportions, weighing 15 to 18 lb. (7 to 8 kg.) and measuring up to 17 or 19 in. (43 or 48 cm.) in length. One of our patients was found, on postmortem examination, to have kidneys the size of footballs—the left weighing 11 lb. (5 kg.) and the right 13 lb. (6 kg.).

It is not unusual to find organs of normal or almost normal size and weight. The clinical and autopsy incidence of polycystic kidney disease as compiled from the literature is shown in the Table.

The surface is irregular and nodular owing to the presence of the cysts which usually appear as translucent vesicles of various sizes. Localized reddened areas may be observed where bleeding has occurred in the cysts. They are closely

9. Norris, R. F., and Herman, L.: Observations on Anatomic Basis of Congenital Polycystic Kidneys, Tr. Am. A. Genito-Urin. Surgeons **31**:41-57, 1938.

10. O'Crowley, C. R., and Martland, H. S.: Association of Polycystic Disease of Kidneys with Congenital Aneurysms of Cerebral Arteries, Tr. Am. A. Genito-Urin. Surgeons **31**:59-68, 1938; Am. J. Surg. **43**:3-9 (Jan.) 1939.

packed together and usually more numerous and larger in the cortical area. They are filled with thin, colorless fluid or after intracystic hemorrhage the contents are thickened and may be almost any color, depending upon the degree of blood disintegration. If a coexisting infection is present, the vesicles may be filled with pus. The chemical analysis of the fluid reveals practically all the components of normal urine.

Histologically the picture depends on the stage of the illness. It is obvious that postmortem examination reveals the terminal stages of the disease. The cysts may involve all parts of the renal parenchyma and little normal tissue is discernible. The recognizable renal parenchyma appears compressed by the cysts, degenerated, and fibrosed, and consequently fewer normal parenchymal components may be observed.

Microscopic examination shows the progressive increase in the size of the cysts, the gradual compression of the parenchyma, pressure atrophy, and fibrosis, while inflammatory changes may be evident or absent. There is also noted a round-cell infiltration.

The cyst walls are lined by cuboidal or flattened epithelium, and the interlobular arteries course underneath this layer; thus, ruptures therein may cause considerable hemorrhage.

It appears that the arterioles are involved in the sclerosing process—the walls appear to be thickened and a diminution in the size of the lumen is noted.[11] Generally there is no communication between the cysts or between the cysts and the renal pelvis. At times a cyst may rupture into the pelvis of the kidney.

Polycystic kidney is not a common disease but is observed with sufficient frequency to merit consideration and to be of clinical importance. The Table indicates the clinical incidence to be approximately 1 in every 4,000 cases. Postmortem statistics indicate that it occurs more frequently than recognized clinically.

The age incidence of polycystic kidneys at the Cleveland Clinic is as follows:

Age in years	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
No. of patients	0	2	8	27	43	12	2	0

The age incidence at the time of first symptoms is as follows:

Age in years	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
No. of patients	0	..	13	31	42	8	0	0

The youngest patient was 18 years of age and the oldest 62. There were 42 men and 52 women.

It may be assumed the actual incidence is approximately 1 to 500 to 750 births. In the series reported by Braasch and Schacht,[3] 98 of the patients were women and 95 men. Davis [3] stated 64.5% of the adult patients were women. Neither race nor color influences the incidence of this disease.

The age at which the disease manifests clinical symptoms is of especial importance. The child not evidencing pronounced destruction of renal parenchyma at birth may lead a normal life up to the second, third, or fourth decade. At this time, owing to more extensive involvement and replacement of renal parenchyma by the

11. (*a*) Schacht, F. W.: Hypertension in Cases of Congenital Polycystic Kidney, Arch. Int. Med. **47**:500-509 (March) 1931. (*b*) Ritter, S. A., and Baehr, G.: Arterial Supply of Congenital Polycystic Kidney and Its Relation to Clinical Picture, J. Urol. **21**:583-592 (May) 1929.

cysts, symptoms appear. Most reports available in the literature reveal that symptoms of sufficient intensity to necessitate medical intervention appear during the fourth and fifth decades of life. Symptoms of less intensity may appear during the third decade. Although it is stated the average age at death is 50 years, many persons live into the sixth or seventh decades with relatively few complaints or symptoms.

Our youngest patient was 18 years of age when first examined, his complaint being hematuria of four days' duration. The oldest was a woman of 62 years whose sole complaint was abdominal distress and weakness, symptoms having been present for only a few months. As seems evident when the disease manifests itself at this late date, the course progresses rapidly and death ensues from uremia within a few years.

In this series, 42 of 94 patients were between 41 and 50 years of age when the presenting symptoms were observed, while for 39 of 94 patients the diagnoses were first established when the patients were between the ages of 41 and 50. It is to be hoped that the more liberal employment of intravenous urography in all instances of "essential hematuria," nephritis, and hypertension will lead to earlier diagnosis; only by this means will polycystic renal disease be recognized while the condition is amenable to prophylactic measures.

Pain and hematuria are the outstanding symptoms and are usually the complaints for which the patient seeks medical advice. The pain is usually located in the flank, may be mild or severe, continuous or colicky in nature, or may be so persistent as to become disabling. Acute renal colic is unusual but may occur during an episode when blood clots pass down the ureter. Thirty of our patients presented the latter symptom but in only a few was it outstanding. Thirty-one patients complained of pain or aching sensations in the flank or abdomen.

Hematuria is usually the symptom that prompts the patient to consult the physician. Were it not for this alarming condition many cases of polycystic renal disease would escape recognition. The renal bleeding is usually of short duration, intermittent, and seldom sufficiently profuse to cause exsanguination. It usually recurs and is instrumental in the production of weakness and anemia. At times the bleeding may be profuse, endangering life and taxing the surgeon's judgment as to the treatment to be instituted.

In one patient of this series, a physician aged 45, abrupt, severe, and prolonged hematuria developed. Finally a Rovsing operation with evacuation of clots from the renal pelvis was performed. The symptoms disappeared, only to recur a few months later, and, because of persistence and severity, nephrectomy was required.

Chills, fever, lassitude, weakness, and loss of weight are among the outstanding secondary symptoms. Thirteen of our patients complained of chills and fever for a few months or weeks preceding examination. In none did this appear as the outstanding symptom. Weakness was the complaint of 65%. In practically all the patients, anemia and retention of nitrogenous products in the blood were noted. Approximately 50% complained of headaches, and in most of these patients hypertension was present.

Macroscopic bleeding was present in 39 (41%) of our patients either at the time of initial examination at the Clinic or at some time in recent months. Walters

and Braasch [12] cited an incidence of 33%.[6] Ten patients (10%) had intermittent episodes of bleeding for periods ranging from 2 to 10 years without roentgenographic investigation.

Of the 55 patients who did not present macroscopic bleeding, microscopic blood cells were found in the urine of 38.

Enlargement of the kidneys is the most important objective finding. It is usually bilateral but frequently is either unilateral or predominantly so, suggesting the presence of a renal neoplasm. Braasch and Schacht [5] reported bilateral enlargement in 151 of 193 cases, unilateral enlargement in 30, and no enlargement in 10.

Ten of our patients had noted the presence of abdominal masses for varying lengths of time, and in one this proved to be the chief complaint.

In our series, bimanual palpation revealed bilateral renal masses in 52 cases (55%). Unilateral enlargement of the kidneys was detected in 24 (25%), no enlargement of the kidneys was observed in 15 (15%), and in 3 cases (3%) examination was not conclusive. Thus in 76 patients (80%) the kidneys or kidney was palpably enlarged. In our series the left kidney appeared enlarged more frequently than the right organ.

Hypertension in the presence of polycystic renal disease has been a subject of considerable discussion. In 1931, Schacht [11a] reported an incidence of 75% in a series of 74 cases submitted to autopsy study.

Since this group (68%) had presented retinal sclerosis, it was concluded that the process is not explainable on a purely renal basis but problably is associated with a generalized vascular disturbance. We noted manometric readings above 145/90 in 69 of our 94 patients (73%). Sixteen of these had symptoms exclusively referable to the hypertension, and the true etiologic diagnosis was made only after complete urologic investigation. Twenty-eight (28%) had normal blood pressures, and in three instances the reading was not recorded (consultations).

Hypertension alone does not explain the repeated attacks of hematuria so characteristic of the disease. In this study it was found that of 69 patients with hypertension 39 had or previously experienced hematuria, while for 30 no history of blood in the urine was elicited. Urinalyses were performed repeatedly in all cases and revealed interesting findings. Red cells, denoting microscopic or macroscopic bleeding, were found in 77 patients. Pus cells in numbers above normal (catheterized specimens having been collected in women and clean voided specimens in men) were demonstrated in 60%. The urine cultures were positive in 26 of 52 cases in which cultures were secured. The organisms most frequently cultured were Escherichia coli, Proteus vulgaris, Staphylococcus albus, and Streptococcus faecalis.

The urine specific gravity was below 1.015 in 58% of the cases and below 1.010 in 30%. The lowest figure was 1.004 and the mean figure 1.013. A low fixed specific gravity is of considerable prognostic significance.

Blood urea values above 40 mg. per 100 cc. of blood were found in 70%, above 60 mg. in 35%, and above 80 mg. in 15%. In contrast to the high percentage of elevated blood urea levels, the number of patients presenting symptoms referable to uremia is remarkably low. The explanation of this discrepancy lies in the fact that nitrogen retention develops slowly, thereby permitting the patient sufficient

12. Walters, W., and Braasch, W. F.: Surgical Aspects of Polycystic Kidney: Report of 85 Surgical Cases, Surg., Gynec. & Obst. **58**:647-650 (March) 1934.

time to adjust to such higher values. A similar contrast may at times be observed in men who have bladder neck obstruction, a gradual process extended over a long period. The gradual development of renal impairment permits the patient to live a normal life for many years.

In spite of the fact that gross hematuria was present in over 41% of the patients, hemoglobin values of 75% (11.5 gm.) were observed in 77%, while the hemoglobin was below 75 (11.5 gm.) in 23%. The lowest figure was 58%, the highest 98%. Low values frequently were observed with either prolonged renal bleeding or a noticeable retention of nitrogenous products.

A careful roentgenographic examination is essential in all cases of suspected polycystic disease. The initial roentgenogram reveals not only renal enlargement but coexisting pathologic lesions, such as calculi or abnormality of the bones. Intravenous urography is usually the procedure of choice, providing the blood urea is within fairly normal limits. In the presence of a more pronounced elevation of the blood urea, little visualization of the dye is observed. In this group receiving adequate medical treatment, the blood urea may be reduced further prior to securing the intravenous urogram. Several patients in this series were managed in this manner, and usually diagnostic films were obtained. In 65 cases excretory urography was performed. In 33 instances definite diagnoses were established from the roentgenograms. In 17 additional cases, tentative diagnoses were established, and in 15 cases there was insufficient concentration of the dye for diagnostic purposes.

Retrograde pyelography is the procedure of choice in the establishment of the diagnosis. It was performed in 56 cases, and correct diagnoses were evident in 51 instances. In none of the patients did we observe untoward reactions directly attributable to the procedure, even though the majority had simultaneous bilateral pyelograms.

The roentgenographic diagnosis of polycystic kidneys may be extremely difficult early in the course of the disease. When the cysts are small, renal enlargement may not be discernible and the pelves are practically normal in size and shape.

As the cysts increase in number and size, the kidney shadow is enlarged visually and the pelvis becomes enlarged and distorted. The calices are deformed, angulated, and elongated. Later the typical "dragon deformity" results. Unquestionably the most important diagnostic feature is the bilaterality of the deformity in polycystic kidneys.

Almost any pathologic lesion may be found associated with polycystic kidneys. Those most frequently observed are hydronephrosis, pyonephrosis, and pyelonephritis. Tumors and calculi are observed less frequently. Melicow [13] in a review of the literature reported one case of hypernephroma associated with polycystic kidneys he had observed. Hemorrhage may, by its intensity and duration, constitute a major complication demanding immediate attention. The association of polycystic kidneys with other congenital anomalies of the kidney is rare. Botez (cited by Gutierrez [14]) in 1912 cited two cases of polycystic disease in horseshoe kidneys.

13. Melicow, M. M., and Gile, H. H.: Hypernephroma in Polycystic Kidney: Review of Literature and Report of Case, J. Urol. **43**:767-773 (June) 1940.

14. Gutierrez, R.: The Clinical Management of Horseshoe Kidney: A Study of Horseshoe Kidney Disease, Its Etiology, Pathology, Symptomatology, Diagnosis and Treatment, New York, Paul B. Hoeber, Inc., 1934.

One of our patients presented a congenital stricture at the ureteropelvic junction, necessitating a plastic operation. As mentioned previously, our incidence of infection was rather high. However, perinephritis was noted in only one patient. In another, severe infection of several large cysts was treated by the Rovsing operation. Calculosis was observed in 9 instances, pyelonephritis in 11, abscess in 1, and unilateral hydronephrosis in 7. Severe hemorrhage occurred in 5 patients.

If the condition is kept in mind, the diagnosis is not usually difficult to establish in moderate or advanced cases. In the early phases, the disease may not be suspected either because of absence of symptoms or because of inability to palpate the kidneys at the time of physical examination. At this stage of the disease, the diagnosis may be established only by urography.

The family history must be investigated in detail, and at times it may give a clue to the diagnosis in view of the family incidence. A personal history of intermittent hematuria, abdominal or flank pain, and chills and fever, although not diagnostic, suggest the possibility of renal disease demanding complete urologic examination.

Bilateral renal enlargement is also suggestive of polycystic disease. When the enlargement is unilateral, the disease must be differentiated from a neoplasm of the kidney. Hypertension, when present, requires urologic survey to eliminate not only unilateral renal pathology but also polycystic disease. In four patients with hypertension referred to us, polycystic kidneys were diagnosed by retrograde pyelography.

Urinalysis, renal function tests, and blood studies are of little value early in the course of the disease. However, the demonstration of impaired renal function suggestive of Bright's disease may lead to roentgenographic study which will establish the true diagnosis.

Roentgen studies, by either intravenous or retrograde technic, constitute the most important procedure by which to detect upper urinary tract disease. All patients in this series were subjected to one or the other of the diagnostic procedures or to a combination of the two.

The clinical course of the disease pursues a fairly constant pattern. At birth, a child with minimal involvement of the kidneys by cysts appears normal. In early adult life he pursues normal activities, but the cysts enlarge, compressing renal parenchyma, and between the ages of 25 and 35 years symptoms first appear. From this period the disease appears to become more active and progressive. Even during midlife the patient may not be incapacitated. The woman patient who marries may become pregnant and pass through this period without untoward results. Of our 51 women patients, 42 had from one to nine pregnancies, and the complications did not appear more numerous than for the average normal woman. I believe, however, that repeated pregnancies should be discouraged because of the added burden on the already affected kidneys as well as the possibility of transmitting the disease to the children.

Operative procedures, aside from those performed on the kidneys, are well tolerated and should be performed unless there is a marked improvement of renal function. Twenty patients in this group sustained from one to three operations without complications. These procedures varied from simple appendectomy or herniorrhaphy to major operations, such as total hysterectomy or colectomy.

After the symptoms become evident, the course of the disease is slow and progressive with occasional exaggeration of the symptoms. During this period the disease simulates Bright's disease. Later, symptoms of renal failure appear, and the patient dies in uremic coma.

The periods of "activity" are characterized by hematuria, pain, and nitrogenous retention. Such episodes may last for days or weeks; they are followed by periods of remission that may last for months, during which time the patient appears definitely improved. A woman patient we have followed for 10 years is a typical example. At the present time this patient is 48 years of age and has been hospitalized on eight different occasions, almost exclusively for hematuria. During the attacks of renal bleeding, her blood urea becomes elevated and the hemoglobin content of the blood drops to values below 60%. The condition is indicative of a terminal state; however, with bed rest and blood transfusions the symptoms subside. In two to three weeks the patient returns to her regular work, is free of discomfort, and leads a normal life until the next episode of bleeding.

An analysis of 87 cases followed closely until recently reveals that 72 patients are living—28 in excellent health and actively engaged in work and 37 in fair condition clinically, although the blood pressures and blood ureas are steadily mounting. Seven patients are in poor health and practically helpless. The average age in this group is 43 years.

Of the 15 patients known to have died at the time of this study, 66% of the fatalities were due to uremia. The average age at death was 50 years. It is worthy of note that for two diagnoses were made elsewhere, 14 and 16 years respectively, before death.

The treatment of polycystic disease is preferably medical, but surgical intervention may be necessary. Neither type of treatment is curative, but therapy is instituted to prevent or to deal with the complications that sooner or later menace the life of the individual.

Renal surgery in polycystic renal disease must be approached with caution to avoid complications which may prove fatal. Meltzer,[15] in 1929, through questionnaires sent to members of the urological association, compiled three surgical cases. Fifty per cent of the patients had died at the end of two years. Lowsley, in discussing Meltzer's paper, said: "The less one does in the way of a surgical or traumatic nature for these patients the better off they are." However, despite this observation, certain complications must be dealt with surgically if the patient's life is to be saved.

The prerequisite for successful surgery is adequate renal function. Function may be improved prior to operation by intravenous administration of fluids and blood transfusions. If possible, the blood urea should be reduced below 60 mg. per 100 cc.

The two direct important surgical indications are hematuria and pain. Infection of the cysts may also indicate operative intervention. Profuse, continuous bleeding which cannot be controlled by conservative medical procedures may necessitate nephrectomy when the bleeding is unilateral in character. In such cases, the function of the remaining kidney must be capable of maintaining life.

A patient with persistent and disabling pain which is unbearable, necessitating continuous use of opiates for relief, may require surgical intervention. In such

15. Meltzer, M.: Surgical Polycystic Kidney, Am. J. Surg. **7**:420-423 (Sept.) 1929.

cases, the Rovsing operation may be advised. Other conditions which indicate operation are perinephritic abscess, calculosis, tuberculosis, or tumors. When the calculus is not obstructing the ureteropelvic junction or is asymptomatic, conservative treatment is indicated. Infections in the form of pyelonephritis, intracystic infection, or perinephritis usually respond to the newer chemotherapeutic agents.

Needle aspiration of noninfected cysts may at times give relief from pain. This measure was successfully employed on four occasions on one of our patients. Failure to secure relief by this simple procedure suggests more radical surgery. Nephrectomy was performed in three instances; one for a large branching calculus and pyonephrosis, one for carcinoma of a polycystic kidney, and one for profuse, uncontrollable bleeding. The three patients are living and well two, six, and five years, respectively.

Incision and drainage of the cysts were performed in eight instances. The indications were pain and infection or pain and profuse hematuria. All eight patients have been living from four to seven years. There were no cases of persistent urinary fistula. Two patients have subsequently been admitted for medical treatment.

Two plastic operations on the ureteropelvic junction were performed on a woman presenting early polycystic disease and hydronephrosis. The result has been satisfactory so far for six years.

The youngest patient subjected to operation was 27 years of age and the eldest was 54.

Medical treatment is indicated for any complication present or which may ensue. The patients are informed of the condition that exists in order to secure complete cooperation and are instructed to drink an abundance of water and to avoid exposure to infections and to cold. The diet suggested should be bland, low in proteins, and rich in vitamins. In the presence of anemia, iron and liver preparations should be prescribed. If the anemia is more pronounced, blood transfusions are of inestimable value. In the presence of retention of nitrogenous products, bed rest and intravenous administration of dextrose are advisable.

Patients with polycystic renal disease should be under strict medical supervision. Measures should be instituted to prevent the usual complications.

With our present knowledge of blood chemistry and newer chemotherapeutic agents, the morbidity and mortality for surgical procedures of a general nature, or confined to the urinary tract, have been reduced to a minimum.

SUMMARY AND CONCLUSIONS

Ninety-four cases of congenital polycystic kidney disease observed at the Cleveland Clinic from January, 1935, to January, 1951, are analyzed.

The condition is congenital, usually bilateral, and progressive in nature.

The clinical incidence is approximately 1 to 4,000 cases; the actual incidence probably 1 to 500 or 1 to 750 births.

The average age diagnosis was established was 43.8 years. The youngest patient was 23 years of age, the oldest 62.

Macroscopic hematuria was present in 39 patients (41%), and abdominal pain was experienced in 61 cases (64%).

Bilateral renal enlargement was found in 52 cases (55%), unilateral in 24 (25%), and no enlargement to palpation occurred in 15.

Hypertension was present in 69 cases (73%), while the blood pressure was normal in 28 (27%).

Blood urea values above 40 mg. per 100 cc. occurred in 70%.

Intravenous urograms proved diagnostic in 33 instances in 65 cases in which urograms were secured, and a tentative diagnosis was made in 17 additional cases.

Retrograde pyelography was performed in 56 cases and proved diagnostic in 51 cases.

Polycystic kidneys do not incapacitate the patient until the late stages of the disease. Of 46 women in this series, 37 had normal pregnancies.

In this group of 94 patients, 15 are known to have died. The majority of the fatalities were caused by uremia. The average age at death was 50 years.

General operative procedures and surgery confined to the urinary tract are frequently required. Adequate preoperative preparation reduces the morbidity and mortality to a minimum. There were no deaths in this series in which surgical treatment was instituted.

Medical treatment is advocated in the majority of cases of polycystic kidney disease.

MUSCLE PEDICLE BONE GRAFTS

Experimental Study

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IN A SERIES of experiments on mongrel dogs, we attempted to compare the reaction and fate of cancellous bone transplanted as a free graft with the reaction and fate of cancellous bone transplanted with a muscle pedicle. The pedicle bone graft was transplanted within the limit of the blood supply of its muscle pedicle and without disturbing the periosteal attachment of the muscle to the bone. If the muscle pedicle was of sufficient width, not too long, and not stretched or twisted, the cut surface of the attached bone graft continued to bleed.

Hellstadius [1] transplanted pedicle bone grafts on a number of rabbits. For his experiments he obtained the grafts from the radius and greater trochanter. His conclusion was that there was no particular difference in the fate of pedicle bone grafts and that of nonpedicle bone grafts. However, he had used cortical or cancellous bone with a pedicle dissected from the tendinous insertion of the muscle. These grafts should have had relatively avascular pedicles.

EXPERIMENTAL PROCEDURE

Six dogs were used for the experiments. Their ages varied from 6 to 9 months. They were fed horsemeat, milk, water, and dried commercial dog food.

Anesthesia for all the operations consisted of pentobarbital (nembutal®) injected intravenously.

The left hip was approached through an anterior incision, after which the adjacent surfaces of the head of the femur and the acetabulum were denuded. A piece of bone, 1.5 by 3 cm., was stripped subperiosteally and removed from the anterior surface of the iliac crest. It was then transplanted across the hip joint as a free graft. Fixation of the graft was achieved by a vitallium® screw inserted into the head of the femur and a vitallium® screw placed in the acetabular rim. An intertrochanteric osteotomy was then done. The wound was closed in layers with catgut sutures.

The right hip joint was likewise approached through an anterior incision. The subperiosteal stripping was carried out on the medial side of the iliac crest without disturbing the origin of the tensor fascia femoris muscle and anterior fibers of the gluteus medius muscle. A piece of bone, 1.5 by 3 cm., was then resected from the anterior surface of the iliac crest, the resection being carried out from within outward. The muscle remaining attached to this piece of bone was fashioned into a short pedicle by sharp dissection. The adjacent surfaces of the anterior portion of the head of the femur and the acetabulum were denuded, and the pedicle bone graft

1. Hellstadius, A.: On the Ability of Bone Tissue (Including Os Novum) to Survive in Pedicle Bone Grafts, Acta chir. Scandinav. **86**:85-109, 1942.

was fixed across the hip joint by vitallium screws inserted into the head of the femur and the acetabular rim. An intertrochanteric osteotomy was then done. The wound was closed in layers with catgut sutures.

A sterile dressing was placed over the wound on either side. Then a double spica plaster cast was applied over sheet wadding. The bilateral intertrochanteric osteotomies had been done to aid in immobilization of the grafts and to facilitate plaster fixation.

No fluid or blood replacement was used during or after operation. For the first seven postoperative days 300,000 units of procaine penicillin were given parenterally each day. The casts were removed in six weeks unless the animals were killed before that time.

GROSS AND MICROSCOPIC FINDINGS AT AUTOPSY

Dog 1 was killed one and a half weeks after operation. The free graft on the left side was easily removed from the surrounding muscle and underlying bone. There was no gross evidence of callus. Microscopic examination showed a loose trabecular system of lamellar bone with intervening marrow elements, some of which had retracted from the trabeculae. No osteoblastic or osteoclastic activity was noted. Most of the lacunae were empty. However, a few were filled with debris. The marrow cells contained poorly staining nuclei and the cell borders were indistinct.

On the right side the muscle pedicle graft appeared healthy. There was no gross evidence of union or callus between the graft and the recipient area. Microsections showed a trabecular system of lamellar bone with normal-appearing marrow elements between the trabeculae. There was little evidence of osteoblastic activity. No osteoclasts were seen. Most of the lacunae had normal-appearing osteocytes in situ. The marrow elements appeared relatively normal.

The essential difference in the grafts on the two sides was that the muscle pedicle graft had the gross appearance of live bone with normal marrow elements, whereas the free graft revealed dead lamellar bone which had not yet undergone osteoclastic revision.

Dog 2 (Figs. 1 and 2) was killed three weeks postoperatively. The free bone graft on the left side could be stripped from the surrounding tissue and had the gross appearance of dead bone. It had not healed to the recipient bone, and showed evidence of much absorption. The surface of the graft appeared rough and moth-eaten. Microscopic examination disclosed irregular trabeculae of lamellar bone with intervening granulation tissue. There were no normal-appearing marrow elements. A little osteoclastic, but no osteoblastic, activity was noted. Many lacunae were empty; others contained poorly staining, eccentrically located osteocytes. The spaces between the trabeculae were filled with vascular connective tissue which contained scattered infiltrations of round cells.

On the right side the muscle attached to the pedicle graft was partly healthy and partly necrotic. The graft had the appearance of normal bone and was firmly attached by fibrous tissue to the head of the femur and the acetabulum. Microscopic study showed a trabecular system of lamellar bone. The marrow spaces were filled with connective tissue elements. There was a little osteoblastic activity, but no osteoclasts were identified. The trabeculae had a few areas of empty lacunae. Other areas contained normal-appearing osteocytes. Most of the marrow spaces were filled with loose connective tissue in which there were many blood vessels and no infiltration of round cells.

The essential difference in the two sides was that grossly the free graft appeared to be dead, while the pedicle graft appeared to be viable. Microscopically, most of the trabeculae of the pedicle graft appeared to contain live osteocytes, whereas in the free graft no healthy-appearing osteocytes were seen. Revascularization of marrow elements had taken place in the bone of both grafts. Osteoblastic activity had begun in the pedicle graft, but not in the free graft. There were more blood vessels and round-cell infiltration in the free graft than in the pedicle graft. This probably means there was more inflammatory reaction in the free graft.

Fig. 1 (Dog 2).—Free graft.

Dog 3 (Figs. 3 and 4) was killed four weeks after operation. The free graft on the left side had retracted from the femur and was not united to the acetabulum. Microscopic examination revealed a few trabeculae of lamellar bone with intervening connective tissue of vascular reactive type. There was little osteoclastic and much osteoblastic activity. The trabeculae of lamellar bone contained mostly empty lacunae.

On the right side the muscle pedicle graft had also retracted from the femur, but appeared to be united to the acetabulum. There was healthy-appearing muscle attached to the graft. Microscopic study showed dense lamellar bone adjacent to dense fibrous bone. No osteoblasts or osteoclasts were seen. The fibrous bone

blended with the lamellar bone. Normal-appearing osteocytes were present in the fibrous bone, and the lamellar bone contained lacunae, most of which were empty. There were small marrow spaces which were filled with loose vascular connective tissue.

There was no essential difference in the microsections of the two grafts. However, grossly the pedicle graft was attached to the acetabulum, while the free graft was not.

Fig. 2 (Dog 2).—Pedicle graft.

Dog 4 was killed six weeks after operation. The free graft on the left side was not attached to the femur, but was united to the acetabulum. Microscopic study showed large trabeculae of fibrous bone with small intervening areas of vascular and highly cellular connective tissue. There was much osteoblastic activity. No trabeculae of lamellar bone were seen.

On the right side the muscle pedicle graft was not united to the recipient area, but appeared healthy. Microsections revealed many trabeculae of lamellar bone with loose connective tissue between the trabeculae. Many of the lacunae were empty. In others the osteocytes were eccentrically located and had stained poorly. Much new bone formation was noted at the periphery of the trabeculae.

Grossly, the free graft was adherent, while the pedicle graft was not. Microscopically, there was much lamellar bone in the pedicle graft, whereas all of the free bone graft had undergone osteoclastic revision. Bone grafts showed pronounced osteoblastic activity.

Dog 5 was killed eight weeks after operation. The free graft on the left side appeared to be replaced largely by fibrous tissue and was firmly adherent to the acetabulum and head of the femur. Microscopic examination revealed a small amount of fairly dense fibrous bone with small intervening marrow spaces. The

Fig. 3 (Dog 3).—Free graft.

marrow spaces were filled with loose connective tissue which had a good blood supply. Many osteoblasts were noted at the margin of the bone trabeculae.

On the right side the muscle pedicle graft was firmly attached by fibrous tissue to the recipient area. Microscopic study disclosed mostly fibrous bone with a few small trabeculae of lamellar bone. There was considerable osteoblastic activity manifested by new bone and osteoid formation. The fibrous bone contained normal-appearing osteocytes, and in the lamellar bone there were empty lacunae. The marrow spaces were small and filled with loose connective tissue and blood vessels.

The essential difference in the gross appearance of the two sides was that there was more bone present in the pedicle graft than in the free graft. Microscopically,

all of the free graft had undergone osteoblastic revision, whereas most, but not all, of the pedicle graft had been revised.

Dog 6 was killed 10 weeks after operation. The free graft on the left side had been absorbed from the femur, but appeared to be solidly healed to the acetabulum. Microscopic examination showed the graft to be composed of dense fibrous bone which had small marrow spaces filled with loose connective tissue. The osteocytes for the most part stained well. There was a great deal of osteoblastic and osteoclastic activity.

Fig. 4 (Dog 3).—Pedicle graft.

The pedicle graft on the right side had become detached from the femur, but appeared to be solidly healed to the acetabulum. Microscopic examination disclosed, principally, a loose trabecular system of lamellar bone. The large spaces between the trabeculae were filled with loose connective tissue and blood vessels. The trabeculae for the most part had pale-staining centers with empty lacunae. This connective tissue was not cellular. Many osteoblasts were forming new bone around the periphery of most of the trabeculae.

There was essentially no difference in the gross appearance of the two grafts. Microscopically, the pedicle graft had much lamellar bone, while the free graft had none.

COMMENT

Although it is difficult to evaluate the microscopic appearance of transplanted cancellous bone, it is our opinion that cancellous bone transplanted as a free graft reacts differently from cancellous bone transplanted with a muscle pedicle which permits adequate circulation. In some instances the cancellous bone graft received enough blood through its muscle pedicle to maintain cellular viability until revascularization could be accomplished from the surrounding recipient area. In other instances the lamellar bone persisted longer when the graft was of the muscle pedicle type than it did when the graft was of the free type.

SUMMARY AND CONCLUSIONS

Six mongrel dogs, aged 6 to 9 months, were subjected to transplantations of free cancellous bone grafts on the left hips and muscle pedicle cancellous bone grafts on the right hips. They were killed at periods varying from 1½ to 10 weeks after operation. The grafts on either side were inspected grossly and microscopically.

From our study it is concluded that under favorable conditions a cancellous bone graft retains its viability when it is transplanted with a muscle belly pedicle which leaves its periosteal blood supply intact.

RESECTION OF THE LIVER FOR CARCINOMA

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MOST TUMORS of the liver are secondary lesions representing either direct invasions from malignant conditions in adjacent organs or metastases from more distant lesions. It has been customary to consider liver involvement as evidence of hopelessness of the patient's condition. Under these circumstances, the liver is usually left alone, and the primary growth is attacked, if at all, only with an idea of palliation. There are some cases, however, in which it is possible to resect not only the primary tumor and its regional lymphatics, but also the secondary extension to the liver as well. It is true that operations on the liver carry special hazards due to blood loss, air embolism, and biliary fistulae, but the problems presented are neither insolvable nor is the operation itself necessarily dangerous. A heroic effort of this sort may be justified occasionally if it appears to offer the hopeless patient a reasonably good chance of better prognosis or greater palliation. There are probably many surgeons who at one time or another have carried out procedures of this sort, but relatively few reports are to be found of such operations or their results. The purpose of the present paper is to record three personal cases, the techniques employed in making the liver resections, and the results 15 to 50 months later.

Review of the literature indicates that different techniques of liver resection have been utilized with varying success. Thermal cautery with ligation of the larger vessels has been used, but the possibility of biliary fistula formation at the site of secondary slough of the cauterized tissue is a disadvantage of this method. Holding the liver edge on either side with thumb and fingers, and then tying the cut vessels individually, is sometimes a useful procedure, but this technique is often attended by large blood loss and there is danger of air embolism. Interruption of the hepatic blood supply by temporary occlusion of the hepatic artery and portal vein while the vessels are tied individually or en masse with through-and-through mattress sutures has definite advantages for hemostasis, but it is a potentially hazardous method. Complete interruption of hepatic blood flow may cause a dangerous drop in blood pressure. This danger is attested to by Packard and Stevenson,[1] and Tinker and Tinker.[2] Wangensteen[3] reports a death

1. Packard, G. B., and Stevenson, A. W.: Hepatoma in Infancy and Childhood, Surgery **15**:292-306 (Feb.) 1944.

2. Tinker, M. B., and Tinker, M. B., Jr.: Resection of the Liver, J. A. M. A. **112**:2006-2008 (May 20) 1939.

3. Wangensteen, O. H.: Cancer of the Esophagus and the Stomach: Monograph for the Physician, Sixth of Series on Early Recognition of Cancer, New York, American Cancer Society, Inc., 1951.

from hepatic necrosis 20 hours after operation. In this instance the hepatic circulation was interrupted for 12 minutes while the left lobe was being excised; the clamps were then released and reapplied for 15 minutes while several metastases were being removed from the right lobe. Serious hypotension was not noted during or immediately following surgery, but within a few hours, a shock-like state developed and persisted until death. Raffucci and Wangensteen [4] have shown from studies on normal dogs that interruption of the blood flow to the liver for more than 20 minutes at a time is followed by evidences of necrosis in a large proportion of cases. They caution that only brief intermittent compression for intervals not exceeding two minutes of continuous occlusion should be employed until more clinical information is available and human tolerance to liver anoxia is more definitely known.

Preliminary placement of hemostatic interlocking mattress sutures and excision of the liver segment with a scalpel appears to be the simplest and safest technique. To aid in the prevention of biliary abscess, reperitonealization of the liver by one of a variety of techniques is important. In small wedge resections, this may be done by simple reapproximation of the surfaces. The use of this technique is represented by Case 1.

When large areas of liver are involved, the extent of the resection may prevent simple approximation of the cut surfaces. In some of these cases, the omentum or a redundant mesocolon may be sutured into the defect. Under other circumstances, such as gastric carcinoma with direct invasion into the left lobe of the liver, the omentum may have been resected or the mesocolon may be very short, so that removal of a large portion of the liver may require some other procedure for reperitonealization of the raw area. In some instances, the falciform ligament can be used with advantage to cover the resected surface of the left lobe, as in Case 3.

REPORT OF CASES

Case 1.—C. A., a 56-year-old woman with an eight-month history of epigastric pain and a 31-lb. (14 kg.) weight loss (26% of the body weight), was shown by x-ray examination to have a constricting lesion of the middle third of the body of the stomach with extension to the lesser curvature. Gastric analysis revealed achlorhydria to histamine. At operation a gastric carcinoma was found apparently involving the anterior portion of the left lobe of the liver by direct extension. A subtotal gastric resection was performed with excision of the involved portion of the left lobe of the liver en bloc. The liver resection was wedge-shaped through the full thickness of the organ. This defect was simply closed with through-and-through mattress sutures of No. 20 cotton. Ooze of blood from the closed incision was controlled with gelfoam. Postoperatively, signs suggestive of a right subphrenic abscess developed, but they subsided on conservative management. In retrospect, it appears that the area of resection should have been drained at the time of operation because of the danger of biliary leakage. Pathologic examination of the operative specimen revealed an anaplastic adenocarcinoma of the stomach with extensive necrosis. The lymph nodes were negative.

The liver wedge measured 5 by 4 by 2 cm., with the tumor involving the capsule but not invading the hepatic parenchyma. The patient has remained well, without evidence of tumor recurrence, for over four years.

4. Raffucci, F. L., and Wangensteen, O. H.: Tolerance of Dogs to Occlusion of Entire Afferent Vascular Inflow to the Liver, Surgical Forum of the 1950 Clinical Congress of the American College of Surgeons, Philadelphia, W. B. Saunders Company, 1951, p. 191.

CASE 2.—J. B., a 51-year-old man, had a 10-month history of pain on defecation and a 6-month history of increasing constipation and blood in the stool. On proctoscopic examination he was found to have a circumferential adenocarcinoma of the wall of the rectum at a level 8 cm. from the dentate line. On Oct. 31, 1950, a combined abdominoperineal resection was done, with ligation of the inferior mesenteric artery at its origin and resection of the entire left colon and its mesentery. A single discrete nodule was palpated in the anterior lateral portion of the right lobe of the liver. The remainder of the liver and the other abdominal organs appeared to be free of metastases. For better exposure, a separate right subcostal incision was made, and interrupted interlocking hemostatic sutures of 2-0 silk were placed through the liver with a Mayo-Robeson half-curved needle in a triangular wedge area. The liver wedge was removed, and vessels on the liver surface were individually ligated where indicated. The long ends of the tied sutures were then approximated and tied so as to join the liver surfaces. Sutures were then applied on the inferior surface for complete approximation of the two surfaces. A Penrose drain to the liver site was brought out through a stab wound for nine days.

Convalescence was uneventful, and the patient was discharged on the tenth postoperative day. Pathological examination of the specimens revealed that the primary tumor had invaded through the muscular wall into the surrounding fat. Sections of 19 lymph nodes revealed metastatic tumor in two. The liver segment was 2.5 by 2.5 by 2 cm. in size. Approximately 1 cm. beneath the capsule was a small, 0.5 cm., nodule, which section revealed to be a metastatic adenocarcinoma. In the spring of 1951, a "second look" operation was done and an additional metastasis 1 cm. in diameter was removed from the right lobe of the liver. A "third look" was done on Oct. 1, 1951, at which time a perineal recurrence was excised, but the liver was noted to be free of gross tumor. However, in December, 1951, pulmonary metastases were noted on a chest film. The general condition of the patient has deteriorated, although he is still alive 15 months after the original liver resection.

CASE 3.—L. S., a 73-year-old man, had a six-month history of increasing anorexia and a 30-lb. (13.6 kg.) weight loss. Gastric analysis revealed no free acid with histamine. Gastrointestinal series in October, 1950, revealed a large filling defect in the prepyloric area of the lesser curvature consistent with a carcinoma. On exploration a large gastric carcinoma was seen, with direct invasion into the left lobe of the liver. No distant metastases were detectable. Nine-tenths of the stomach, the spleen, and a large portion of the left lobe of the liver were resected en bloc. To mobilize the left lobe of the liver, the triangular ligament was divided and the falciform ligament was severed close to its attachment to the anterior abdominal wall and the inferior surface of the diaphragm. Interrupted overlapping sutures of 2-0 silk were placed at the medial side of the left lobe of the liver, which was then resected with the stomach. Additional vessels on the surface of the liver were ligated individually. The falciform ligament was then swung over the free surface of the liver as a flap and was sutured to the inferior surface of the liver (Figure). A Penrose drain was placed down to the site after the posterior Hofmeister gastrojejunostomy had been completed. A small amount of biliary drainage continued for 14 days, after which time the drain was removed.

The convalescence of the patient was uneventful. He resumed work and did well for one year but now, 15 months postoperatively, has evidence of recurrence. Thus the procedure was only palliative. Complete reperitonealization of the resection site with the falciform ligament was a help in the management of this patient.

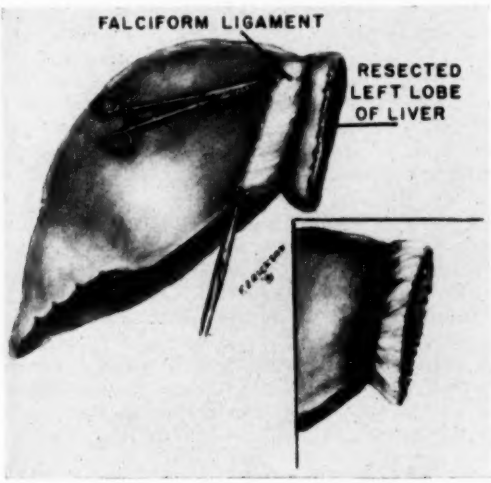
COMMENT

The benefits of resecting the liver en masse with the area of carcinomatous involvement are illustrated by Case 1. A blunt dissection of adherent or invaded surfaces of surrounding organs is as great an error as incision through any other portion of the tumor and should be avoided.

The amount of benefit obtained from the excision of isolated metastases, as illustrated by Case 2, is still problematical. However, little morbidity was occasioned by the procedure, and this should encourage further use and follow-up reports of this type of case so that the true value of the procedure may be better evaluated.

In general, excision of liver metastases from the colon should offer relatively good outlook as compared to gastric carcinoma, because as a rule colon carcinoma is a less highly malignant tumor.

Massive liver resection, as illustrated by Case 3, should have its best outlook in cases with direct invasion of the liver, but it has also been used in cases with extensive metastases. Wangensteen [3] has reported the excision of the entire right lobe of the liver, which was completely replaced by metastases from a carcinoma of the stomach. The operation was undertaken as a "second look" operation seven months after gastric resection. Hemostatic clamps were placed on the hepatic and superior mesenteric arteries as well as the portal vein for a period of 33 minutes. A small fragment of capsule remained, which was sutured up against the left lobe of the liver. The patient recovered and survived for seven months.



Technic of utilizing entire falciform ligament for complete reperitonealization of resected left lobe of liver in Case 3. Inset shows completed procedure with falciform ligament covering site of resection.

In the present case reperitonealization after liver resection was accomplished by using the falciform ligament. Previous mention has been made [5] of the use of a portion of the falciform ligament for this purpose, but, as far as we are aware, there have been no previous reports stating that the entire falciform ligament was removed flush with the abdominal wall and used for complete reperitonealization of the resected left lobe of the liver. With this procedure little or no morbidity was occasioned by excision of this large portion of the liver, so that although the procedure proved not to be curative, some palliation may have resulted.

5. Brunschwig, A.: Radical Surgery in Advanced Abdominal Cancer, Chicago, The University of Chicago Press, 1947, p. 223. Altman, W. A.: Resection of Left Lobe of Liver for Benign Hemangioma, J. A. M. A. **146**:254 (May 19) 1951.

SUMMARY AND CONCLUSIONS

Extension of carcinoma to liver does not always indicate hopelessness. In selected cases it is possible to resect the grossly involved portion of the liver as well as the primary growth.

Dangers inherent in operations on the liver can be reduced somewhat by the use of delimiting hemostatic mattress sutures, reperitonealization, and drainage. Methods of reperitonealizing raw surfaces of the liver are discussed.

The operation is justified in that it may offer an otherwise hopeless patient a better prognosis or improved palliation.

Three illustrative cases are reported.

LEIOMYOMA OF THE CARDIOESOPHAGEAL JUNCTION

G. EDWARD SCHNUG, M.D.
SPOKANE, WASH.

IN RECENT years great strides have been made in the development of surgical methods and techniques in caring for patients with carcinoma of the esophagus, esophageal diverticula, and congenital anomalies of the esophagus. Some of the more unusual lesions of the esophagus have not received the same added attention. Among these less frequently discussed lesions are the benign tumors. These lesions are not infrequently found in a patient who is being studied as a carcinoma suspect. It is true that many of the surgical methods used in the treatment of carcinoma of the esophagus are applicable to these benign conditions. However, the benign lesions at times present added interesting and debatable problems in diagnosis and treatment.

According to most authors, leiomyomas are the most common benign tumors found in the esophagus. These lesions, however, are quite rare. In 1934 Moersch and Harrington [1] were able to find only 15 benign esophageal tumors among 11,000 patients complaining of dysphagia. These authors also reported in a review of 7,459 postmortem examinations at the Mayo Clinic that only 44 benign tumors of the esophagus were found. There were 32 leiomyomas among the 44 cases of benign tumor incidentally found at autopsy. Schafer and Kittle [2] found 11 benign esophageal tumors in a series of 6,001 postmortem examinations at the University of Chicago Clinic. Leiomyomas of the cardioesophageal region of the esophagus are exceedingly rare. In 1933 T. Ohsawa [3] reported the first case in which a leiomyoma of the esophagus was successfully removed. This was a small, 1-cm. tumor located at the cardioesophageal region. Brock [4] in 1942 reported the second case of leiomyoma of the cardioesophageal region of the esophagus, and in this case a resection of the esophagus and adjacent stomach was necessary to remove the tumor. These case reports were followed by reports of patients with cardioesophageal leiomyomas by Moersch and Harrington,[1] Schafer and Kittle,[2] and Kenworthy and Welch,[5] each reporting one case with a tumor located in this region. Goldman and Masters [6] in 1952 reported the last case recorded in the literature.

1. Moersch, H. J., and Harrington, S. W.: Benign Tumors of the Esophagus, Ann. Otol. Rhin. & Laryng. **53**:800-817, 1944.

2. Schafer, P. W., and Kittle, C. F.: Esophageal Leiomyoma, J. A. M. A. **133**:1202-1205, 1947.

3. Ohsawa, T.: Surgery of the Esophagus, Arch. jap. Chir. **10**:605-700, 1933.

4. Brock, R. C.: Cardio-Esophageal Resection of Tumor of the Cardia: Report of a Successful Case, Brit. J. Surg. **30**:146-150, 1942.

5. Kenworthy, R. A., and Welch, C. S.: Leiomyoma of the Esophagus and Cardia of the Stomach, Surgery **23**:745-752, 1948.

6. Goldman, A., and Masters, H.: Leiomyoma of the Esophagus, Arch. Surg. **60**:559-575, 1950.

In this communication I wish to add one additional case to this series of six previously reported cases of leiomyoma of the cardioesophageal region.

REPORT OF A CASE

The patient was a 50-year-old married woman, whom I first saw in my office on Aug. 17, 1950. She came in complaining of indigestion characterized by a feeling of fullness in the upper abdomen, frequent belching, and discomfort beneath the sternum. These symptoms first appeared three years prior to my examination. At that time they lasted only a few days and

Fig. 1.—Roentgenogram of barium-filled lower esophagus and stomach showing large diverticulum-like defect in lower esophagus.

apparently cleared up when the patient went on a liquid diet. Following the onset she had intermittent episodes during which time she had the above-described symptoms; usually these episodes would last for about a week. Three weeks prior to her first visit she had a recurrence of the indigestion, upper abdominal fullness, and substernal pain, which seemed to be more severe than the previous attacks. She again went on a bland diet and obtained quite marked relief from her symptoms. Her only significant remaining symptom was a feeling of fullness in the upper abdomen.

Examination revealed a well-nourished, well-developed woman who showed no significant physical abnormalities. No mass was palpable in the upper abdomen. The blood count and urinalysis were both within normal limits. On Aug. 2, 1950, an upper gastrointestinal series

revealed some very interesting and unusual findings in the lower third of the esophagus (Fig. 1). This barium study was repeated on Aug. 19, 1950, and exactly the same findings were present. The radiologist was unable to make a definite diagnosis but described the lesion as follows: "There is an unusual contour of the upper end of the stomach which looks like a herniation of the lower esophagus and adjacent portion of the stomach through a small foramen, probably the gastrohepatic ligament."

Although we did not have a definite diagnosis, I felt that we should make an exploratory examination. I felt that the lesion was most likely some type of diverticulum or outpouching of a weakened esophageal wall. If that were the case, there would always be danger of perforation if the lesion were not corrected. Because of the dependent position of this outpouching of the esophagus, which I interpreted as a diverticulum-like condition, I felt that

Fig. 2.—Postoperative roentgenogram showing widely patent esophagogastric anastomosis.

esophagoscopy might carry some definite danger and did not recommend that this diagnostic procedure be carried out. On Aug. 25, 1950, an exploration was done through an upper left rectus abdominal incision. The patient was prepared and draped so that this incision could be extended up into the chest if necessary. We found a large, hard, nodular tumor occupying the space behind the stomach, including the lower esophagus and completely encircling the abdominal portion of the esophagus. The tumor rested in the retroperitoneal space, extending from the hilus of the liver to the spleen and from the diaphragm down to the upper border of the pancreas. The tumor grossly appeared benign, and this was verified by a frozen section done on a specimen taken at the operating table. The tumor was removed, and at the area where it encircled the esophagus the esophageal wall was found to be greatly attenuated and to consist of only mucosa and submucosa. Because of the marked thinning of the esophageal wall,

it was necessary to resect approximately 2 in. (5 cm.) of the esophagus. The defect in the stomach was closed, and an anastomosis was made between the distal esophagus and the fundus of the stomach. The patient had an uneventful postoperative course and was discharged from the hospital on Sept. 1, 1950, her seventh postoperative day. Since her operation the patient has gotten along very well and has been entirely symptom free. She has noticed a complete relief from the full sensation in the upper abdomen. An upper gastrointestinal series repeated on Sept. 22, 1950, showed a normal esophagus with a widely patent esophagogastric anastomosis (Fig. 2). The patient has continued to remain symptom free and in good health.

PATHOLOGY

The tumor mass weighed 632 gm. It was 15 × 11.5 cm. in surface dimensions (Fig. 3). On sectioning, a calcified area 2.0 × 1.5 cm. in surface dimensions, was found near one border of the mass.

Microscopic Examination.—Sections were taken from a large number of areas after the specimen had been fixed in formalin. The sections were stained by the Masson trichrome method and with hematoxylin and eosin. Everywhere the structures consisted of compactly laid down interlacing bundles of what apparently was smooth muscle. The nuclei in the cells

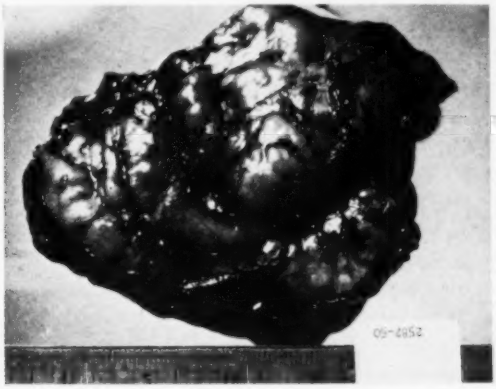


Fig. 3.—Photograph of intact, well encapsulated tumor. Deep groove transversing exposed surface was occupied by remains of esophageal wall.

were elongated and had blunt ends. The nucleoli were small. In some cells there were two nucleoli. The fibers were wavy. No cells were in mitosis. One section was through the wall of the stomach. The mucosa was slightly infiltrated by lymphocytes but it was intact and regular. There was some hyperemia of all layers. In a section of esophagus the surface was covered with a slightly thickened but otherwise regular squamous cell epithelium.

COMMENT

Leiomyomas of the esophagus tend to occur in a slightly younger age group than do malignant growths. The symptomatology of the condition is often difficult to interpret. The symptoms are usually of long standing, usually many years rather than several months, and are slower in their progression. The commonest symptom is dysphagia, but other symptoms such as regurgitation, substernal discomfort, heartburn, upper abdominal discomfort, and bleeding may be present. Tumors that are located in the lower esophagus quite frequently give upper abdominal discomfort. Characteristically these tumors do not ulcerate, and thus pain in relation to eating is not common. Occasionally they do ulcerate, and then pain with

eating or after eating may be present. The diagnosis in these cases depends on the barium study by x-ray and esophagoscopy. The findings on x-ray examination are frequently bizarre, as is demonstrated in this patient. The barium column frequently shows marked angulation, and variations in shape and dimensions of the filling defect may be evident. Actual obstruction of the esophagus is usually absent. The mucosal folds are usually intact and easily visible on fluoroscopy. In this case, a diverticulum-like projection was present in the esophagus. In reviewing the literature, I can find only one previously reported case of leiomyoma of the esophagus with an associated diverticulum. This was an autopsy case reported by Stewart [7] in 1931. Esophagoscopy is of value in differentiating the lesion from other obstructive lesions of the esophagus, particularly carcinoma. The mucosa will usually be found intact, and if no ulceration is found it is usually wise not to do a biopsy in order to avoid the possibility of secondary infection which might complicate the procedure of removal of the tumor.

As was stated earlier, leiomyomas involving the lower esophagus and cardia of the stomach are extremely unusual. In this particular case it was possible to remove the tumor without difficulty by the abdominal route. It was necessary to resect a segment of the esophagus because of damage to the wall of the organ and the marked thinning of the mucosa. In many instances it is advisable to attack these lesions through the transthoracic approach. In most cases cited in the literature on leiomyomas located in other portions of the esophagus, it was possible to remove the tumors by shelling them out, and a resection of the esophagus was not necessary. This, of course, might also apply to some lesions located in the cardioesophageal region, but in those cases which I was able to find recorded in the literature a resection was almost always necessary.

SUMMARY AND CONCLUSIONS

One case of leiomyoma, involving both the lower esophagus and the cardia of the stomach, which was successfully treated by resection and esophagogastric anastomosis, is reported. The abdominal approach was used in this particular case with complete success. This is the sixth reported case of leiomyoma of the cardioesophageal junction and the fourth reported case in which a resection of the lesion was done. These tumors are usually encountered in patients who are being investigated because of obstructive symptoms in the esophagus and are suspected of having carcinoma. The appearance of these lesions on barium study and by esophagoscopy differs markedly from the appearance of malignant lesions of the esophagus. The most characteristic finding is the frequently bizarre appearance of the x-ray photograph on barium studies. These lesions, being benign, are very amenable to surgical therapy, and even though they are rare their importance must be stressed.

7. Stewart, J. D., Jr.: Myoma of the Esophagus with Associated Diverticula, Arch. Path. **12**:77-84, 1931.

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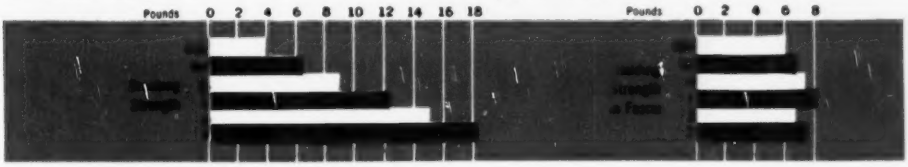

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1. Waters, E. G.: Fine Chromic Catgut in Surgery and Obstetrics, Bull. Margaret Hague Mat. Hosp. 1(4): 102 (Dec.) 1948.

2. Burke, J.: A Consideration of the Suture Problem, American Journal of Surgery, 49:303, 1940.

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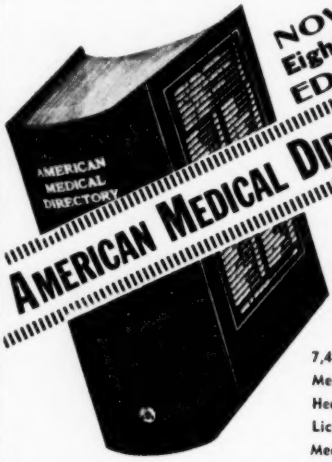

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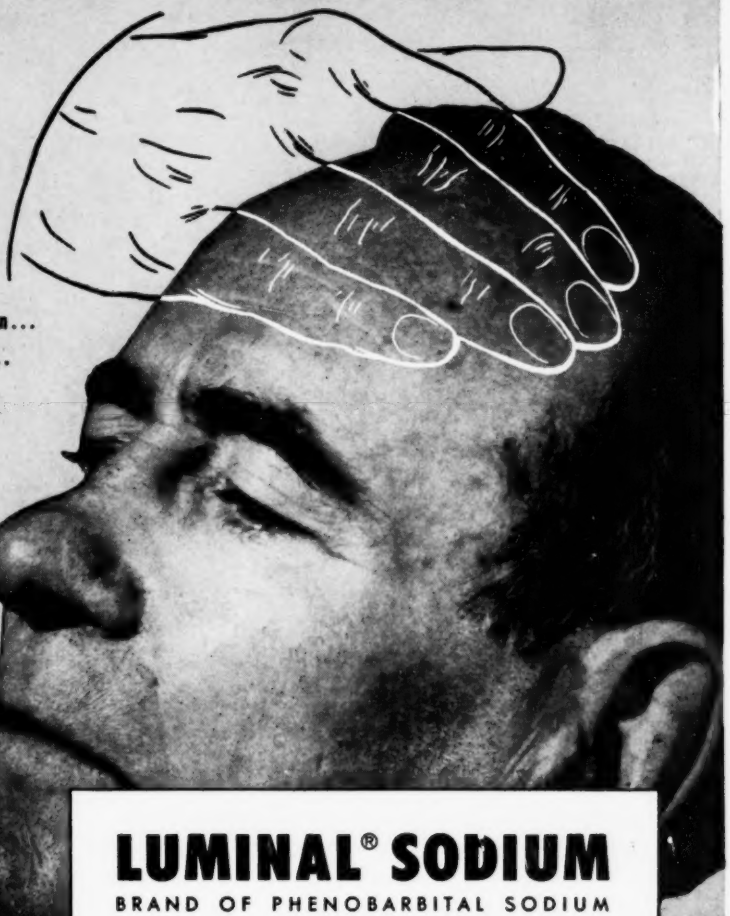

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